

Steps for Self-Injection of GONAL-F[®] RFF* 75 IU

Our original treatment for follicle stimulation in the US

Trust matters

The most prescribed r-FSH
in the United States.

*RFF = revised formulation female.

INDICATIONS

GONAL-F[®] RFF 75 IU (folitropin alfa for injection) is a prescription medicine containing follicle-stimulating hormone (FSH) used in:

Infertile Women To:

- Help healthy ovaries develop (mature) and release an egg to help you get pregnant
- Cause your ovaries to develop multiple (more than one) eggs as part of an Assisted Reproductive Technology (ART) program

IMPORTANT RISK INFORMATION

Do not use GONAL-F RFF 75 IU if you:

- Are allergic to recombinant human FSH or any of the ingredients listed on the product carton or package insert
- Have high levels of FSH in your blood that show your ovaries do not work at all
- Have uncontrolled thyroid, adrenal, or pituitary problems
- Have a tumor in your female organs, including your ovaries, uterus, or breast that may get worse with high levels of estrogen
- Have a tumor in your brain, such as a tumor in your pituitary gland or hypothalamus
- Have abnormal bleeding from your uterus or vagina from an unknown cause
- Have ovarian cysts or large ovaries from an unknown cause

Before you start using GONAL-F RFF 75 IU,

tell your healthcare provider about your medical conditions including if you:

- Have or have had asthma
- Have been told by a healthcare provider that you have an increased risk for blood clots (thrombosis)
- Have ever had a blood clot (thrombosis), or anyone in your family has ever had a blood clot (thrombosis)
- Have had stomach (abdominal) surgery
- Have had twisting of your ovary (ovarian torsion)
- Had or have a cyst on your ovary
- Have polycystic ovarian disease
- Are pregnant or think you may be pregnant. GONAL-F RFF 75 IU is not for pregnant women. Your healthcare provider will give you a pregnancy test before you start using GONAL-F RFF 75 IU.
- Are breastfeeding. It is not known if GONAL-F RFF 75 IU passes into your breast milk. You and your healthcare provider should decide if you will take GONAL-F RFF 75 IU or breastfeed. You should not do both.
- Are not an adult. GONAL-F RFF 75 IU is not for children. It is not known if GONAL-F RFF 75 IU is safe or works in children.

Tell your healthcare provider about all the medicines you take, including prescription

and over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use GONAL-F RFF 75 IU?

- Read the "Instructions for Use" that comes with GONAL-F RFF 75 IU for information about the right way to use GONAL-F RFF 75 IU
- Use GONAL-F RFF 75 IU exactly as your healthcare provider tells you to
- GONAL-F RFF 75 IU is given by injection under your skin. You can inject GONAL-F RFF under the skin in the stomach (abdomen), upper arm, or upper leg.
- Do not inject GONAL-F RFF 75 IU at home until your healthcare provider has taught you the right way to inject it
- Change your injection site as your healthcare provider showed you
- Do not change your dose or the time you are scheduled to use GONAL-F RFF 75 IU unless your healthcare provider tells you to
- If you miss or forget to take a dose, do not double your next dose. Ask your healthcare provider for instructions.
- Your healthcare provider will do blood and urine hormone tests while you are using GONAL-F RFF 75 IU. Make sure you follow-up

with your healthcare provider to have your blood and urine tested when told to do so.

Call your healthcare provider if you have any questions about your dose or how to use GONAL-F RFF 75 IU.

Your healthcare provider may do ultrasound scans of your ovaries. Make sure you follow-up with your healthcare provider to have your ultrasounds.

What are the possible side effects of GONAL-F RFF 75 IU?

GONAL-F RFF 75 IU may cause serious side effects, including:

- **Severe Allergic Reactions.** Women who have used GONAL-F, GONAL-F RFF 75 IU or GONAL-F Redi-ject[®] in the past may have a severe allergic reaction right away when they use GONAL-F RFF again. This severe allergic reaction may lead to death. If you have any of the following symptoms of a severe allergic reaction, stop using GONAL-F RFF and go to the nearest hospital emergency room right away:
 - Shortness of breath
 - Swelling of your face
 - Itchy, red bumps or rash on your skin (hives)
- **Ovarian Hyperstimulation Syndrome (OHSS).** OHSS is both a serious and

common side effect. Using GONAL-F RFF 75 IU may cause OHSS. OHSS is a serious medical condition that can happen when your ovaries produce too many eggs (overstimulated). OHSS can cause fluid to suddenly build up in the area of your stomach, chest, and heart, and can cause blood clots to form. In rare cases OHSS has caused death. OHSS may also happen after you stop using GONAL-F RFF 75 IU. Stop using GONAL-F RFF 75 IU and call your healthcare provider right away if you have symptoms of OHSS, including:

- Trouble breathing
- Severe lower stomach (pelvic) area pain
- Weight gain
- Nausea
- Vomiting
- Diarrhea
- Decreased urine output
- **Lung problems.** GONAL-F RFF 75 IU may cause serious lung problems including fluid in your lungs (atelectasis), trouble breathing (acute respiratory distress syndrome), and worsening of asthma.

Please see Important Risk Information continued on page 2 and accompanying full Prescribing Information, Patient Information, and Instructions for Use (IFU).

How to use GONAL-F RFF* 75 IU

Do not inject GONAL-F RFF* 75 IU at home until your healthcare provider has taught you the right way to inject it. GONAL-F RFF* 75 IU is for injection under the skin of the stomach (abdomen), upper arm, or upper leg. Choose a different injection site each day to minimize irritation.

Please read the following instructions carefully.

PREP:

Before you get started



GONAL-F RFF* 75 IU must be stored in the refrigerator between 36 °F to 46 °F until expiration date. Store away from light.



Wash your hands with soap and water to keep the things you use as clean as possible.



Gather everything you need on a clean, flat surface:

- one vial of GONAL-F RFF* 75 IU
- one prefilled syringe of sterile water for injection, USP (1 mL)
- one **pink** mixing needle (18 gauge)
- one **red** injection needle (29 gauge)
- two alcohol swabs
- one sharps container

Mixing the powder and water to make up your medicine



Using your thumb, flip off the plastic cap of the vial and wipe the top of the vial stopper with an alcohol swab.



Carefully twist and pull off the protective cap of the prefilled syringe of sterile water.



Remove the safety seal cover of the **pink** mixing needle. Twist the needle onto the prefilled syringe until it is tightened, being sure to keep the protective needle cap in place, and then carefully remove the cap.

Do not touch the needle or allow it to touch any surface.



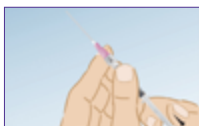
Holding the vial upright with the bottom on a flat surface, insert the needle straight down through the center circle marked on the vial's rubber stopper. Slowly press down on the syringe plunger to inject the sterile water into the vial. Gently rotate the vial between your fingers until the powder is dissolved.

DO NOT shake.



While keeping the needle inserted, lift and turn the vial upside down and pull back the **pink** needle to withdraw the entire contents of the vial. Remove the needle from the vial.

Do not use this needle to inject your dose.



Gently pull the plunger back to allow a small air space. Recap the needle. Twist off the **pink** needle from the syringe and immediately throw away (dispose of) the needle in an FDA-cleared sharps disposal container.

See FAQs for safe disposal of used needles, vial, and syringe.

If your dose requires more than one vial of GONAL-F RFF* 75 IU, use the same **pink needle and syringe now containing the mixture to mix (reconstitute) additional vials.**

Preparing the dose and injection site



Remove the safety seal cover from the **red** injection needle. Twist the needle onto the prefilled syringe until it is tightened, being careful to keep the protective needle cap in place, and then remove the protective cap.

Do not use if the liquid solution is discolored or contains any particles. If this happens, throw it away and call your healthcare provider or pharmacist right away.



With the syringe pointing upward, gently tap on the syringe and slowly push the plunger until all air bubbles are gone and a drop of liquid appears on the tip of the needle.

Do not touch needle or allow it to touch any surface.



Recap the needle and set on a clean, flat surface. The syringe is now ready for administration.

Use GONAL-F RFF* 75 IU immediately after preparing the dose.



Choose an injection site. Clean the skin at your chosen site with the second alcohol swab.

Injecting your dose



Uncap the syringe, then pinch the previously cleaned skin around the injection site with one hand.



GONAL-F RFF* 75 IU is given by injection under your skin. Insert the entire length of the needle into the skin at a 90° angle, then release the pinched skin. Slowly depress the plunger until all medication is injected.



Remove the needle from your skin and put the cap back on. Properly dispose of syringe, vial, and needles in your sharps container immediately after use. Do not reuse or share syringes or needles.

See FAQs for safe disposal of used needles, syringes, and vials.

FAQs

How do I properly dispose of medicine products?

All used needles, syringes, and vials should be discarded in an FDA-cleared sharps disposal container immediately after use.

If you do not have a sharps container, **do not throw away loose needles, syringes, and vials in your household trashcan.** Instead, use a container that is:

- made of heavy-duty plastic
- able to be closed with a tight-fitting, puncture-resistant lid
- upright and stable during use
- leak resistant
- properly labeled to warn of hazardous waste inside the container

For more information, visit www.fda.gov/safesharpsdisposal.

Can I still use my medication if I left it outside in a car during hot or cold weather?

GONAL-F RFF* 75 IU must be stored away from light. Vials (mixed or unmixed) can be stored in the refrigerator, between 36°F to 46°F, or at room temperature, between 68°F and 77 °F.

For more information about storing your medication, call Fertility LifeLines™ support at 1-866-538-7879 or contact your healthcare provider.



MORE SUPPORT

Scan the QR code to watch an injection video for GONAL-F RFF* 75 IU (follitropin alfa for injection)

For more support materials, visit EMDSeronoFertility.com.

*RFF = revised formulation female.

IMPORTANT RISK INFORMATION (continued)

- **Blood clots.** GONAL-F RFF 75 IU may increase your chance of having blood clots in your blood vessels. Blood clots can cause:
 - Blood vessel problems (thrombophlebitis)
 - Stroke
 - Loss of your arm or leg
 - Blood clot in your lung (pulmonary embolus)
 - Heart attack
- **Twisting (torsion) of your ovary.** GONAL-F RFF 75 IU may increase the chance of your ovary twisting if you already have certain conditions such as OHSS, pregnancy and previous abdominal surgery. Twisting of your ovary may lead to blood flow being cut off to your ovary.
- **Ovaries that are too large.** GONAL-F RFF 75 IU may cause your ovaries to be abnormally

large. Symptoms of large ovaries include bloating or pain in your lower stomach (pelvic) area.

- **Pregnancy with and birth of multiple babies.** GONAL-F RFF 75 IU may increase your chance of having a pregnancy with more than one baby. Having a pregnancy and giving birth to more than 1 baby at a time increases the health risk for you and your babies. Your healthcare provider should tell you about your chances of multiple births.
- **Birth defects.** A baby born after an ART cycle may have an increased chance of having birth defects. Your chances of having a baby with birth defects may increase depending on:
 - Your age
 - Certain sperm problems

- Your genetic background and that of your partner
- A pregnancy with more than 1 baby at a time

Ectopic pregnancy (pregnancy outside your womb). GONAL-F RFF 75 IU may increase your chance of having a pregnancy that is abnormally outside of your womb. Your chance of having a pregnancy outside of your womb is increased if you also have fallopian tube problems. Call your healthcare provider right away if you have symptoms of an ectopic pregnancy including:

- Stomach or pelvic pain especially on one side
- Shoulder pain
- Neck pain
- Rectal pain
- Nausea and vomiting

Miscarriage. Your chance of loss of an early pregnancy may be increased if you had difficulty becoming pregnant.

Tumors of the ovary. If you have used medicines like GONAL-F RFF 75 IU more than one time to get pregnant, you may have an increased chance of having tumors in your ovary(ies) (including cancer).

Common side effects of GONAL-F RFF include:

- Headache
- Stomach pain
- Stomach bloating
- OHSS
- Swelling and pain at the injection site
- Diarrhea
- Nausea
- Gas

- Ovarian cyst

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of GONAL-F RFF 75 IU. For more information, call your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please see full Prescribing Information, Patient Information, and IFU for GONAL-F RFF* 75 IU provided with this tear pad and in your product carton, or visit online.

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 ($\geq 2\%$) 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 ($\geq 2\%$) 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*

1 INDICATIONS AND USAGE

- 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 Assisted Reproductive Technology (ART) Cycles

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Dosage and Administration Information
- 2.2 Preparation of GONAL-F RFF and Selection of Injection Site
- 2.3 Dosing for Induction of Ovulation
- 2.4 Dosing for Multiple Follicle Development as part of an Assisted Reproductive Technology (ART) Cycle
- 2.5 Missed Dose

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

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

- 5.11 Laboratory Tests

6 ADVERSE REACTIONS

- 6.1 Clinical Study Experience
- 6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Induction of Ovulation (OI)
- 14.2 Development of Multiple Follicles as a part of an Assisted Reproductive Technology (ART) Cycle

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

*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 $\geq 2\%$ 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 $\geq 2\%$ 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 overdose [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 μ g) 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

^aCumulative rates were determined per woman over cycles 1, 2, and 3.

^bNon-inferior to comparator recombinant human FSH based on a two-sided 95% confidence interval, intent-to-treat analysis.

^cSecondary efficacy outcomes. The trial was not powered to demonstrate differences in these outcomes.

^dClinical 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 1/2" 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:
EMD Serono, Inc.
Rockland, MA 02370 U.S.A.

PATIENT INFORMATION
GONAL-F® RFF (gon-AL-eff ar-eff-eff)
(follitropin alfa injection)
for subcutaneous use

What is GONAL-F RFF?

GONAL-F RFF is a prescription medicine containing follicle-stimulating hormone (FSH).

GONAL-F RFF is used in:

infertile women to:

- help healthy ovaries develop (mature) and release an egg to help you get pregnant
- cause your ovaries to make multiple (more than 1) eggs as part of an Assisted Reproductive Technology (ART) program

Do not use GONAL-F RFF if you:

- are allergic to recombinant human FSH or any of the ingredients in GONAL-F RFF. See the end of this leaflet for a complete list of ingredients in GONAL-F RFF.
- have high levels of FSH in your blood that show your ovaries do not work at all.
- have uncontrolled thyroid, adrenal, or pituitary problems.
- have a tumor in your female organs, including your ovaries, uterus or breast that may get worse with high levels of estrogen.
- have a tumor in your brain, such as a tumor in your pituitary gland or hypothalamus.
- have abnormal bleeding from your uterus or vagina from an unknown cause.
- have ovarian cysts or large ovaries from an unknown cause.

Before you start using GONAL-F RFF tell your healthcare provider about all of your medical conditions, including if you:

- have or have had asthma
- have been told by a healthcare provider that you have an increased risk for blood clots (thrombosis)
- have ever had a blood clot (thrombosis), or anyone in your family has ever had a blood clot (thrombosis)
- have had stomach (abdominal) surgery
- have had twisting of your ovary (ovarian torsion)
- had or have a cyst on your ovary
- have polycystic ovarian disease
- are pregnant or think you may be pregnant. GONAL-F RFF is not for pregnant women. Your healthcare provider will give you a pregnancy test before you start using GONAL-F RFF.
- are breastfeeding. It is not known if GONAL-F RFF passes into your breast milk. You and your healthcare provider should decide if you will take GONAL-F RFF or breastfeed. You should not do both.
- are not an adult. GONAL-F® is not for children. It is not known if GONAL-F is safe or works in children.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use GONAL-F RFF?

- Read the "**Instructions for Use**" that comes with GONAL-F RFF for information about the right way to use GONAL-F RFF.
- Use GONAL-F RFF exactly as your healthcare provider tells you to.
- GONAL-F RFF is given by injection under your skin. You can inject GONAL-F RFF under the skin in the stomach (abdomen), upper arm, or upper leg.
- **Do not** inject GONAL-F RFF at home until your healthcare provider has taught you the right way to inject it.
- Change your injection site as your healthcare provider showed you.
- **Do not** change your dose or the time you are scheduled to use GONAL-F RFF unless your healthcare provider tells you to.
- If you miss or forget to take a dose, do not double your next dose. Ask your healthcare provider for instructions.
- Your healthcare provider will do blood and urine hormone tests while you are using GONAL-F RFF. Make sure you follow-up with your healthcare provider to have your blood and urine tested when told to do so.
- Call your healthcare provider if you have any questions about your dose or how to use GONAL-F RFF.
- Your healthcare provider may do ultrasound scans of your ovaries. Make sure you follow-up with your healthcare provider to have your ultrasounds.

What are the possible side effects of GONAL-F RFF?

GONAL-F RFF may cause serious side effects, including:

- **severe allergic reactions.** Women who have used GONAL-F®, GONAL-F® RFF or GONAL-F® Redi-Ject® in the past may have a severe allergic reaction right away when they use GONAL-F RFF again. This severe allergic reaction may lead to death. If you have any of the following symptoms of a severe allergic reaction, stop using GONAL-F RFF and go to the nearest hospital emergency room right away:
 - shortness of breath
 - swelling of your face
 - itchy, red bumps or rash on your skin (hives)
- **ovarian hyperstimulation syndrome (OHSS).** OHSS is both a serious and common side effect. Using GONAL-F RFF may cause OHSS. OHSS is a serious medical condition that can happen when your ovaries produce too many eggs (overstimulated). OHSS can cause fluid to suddenly build up in the area of your stomach, chest, and heart, and can cause blood clots to form. In rare cases OHSS has caused death. OHSS may also happen after you stop using GONAL-F RFF. Stop using GONAL-F RFF and call your healthcare provider right away if you have symptoms of OHSS, including:
 - trouble breathing ○ severe lower stomach (pelvic) area pain ○ weight gain
 - nausea ○ vomiting
 - diarrhea ○ decreased urine output
- **lung problems.** GONAL-F RFF may cause serious lung problems including fluid in your lungs (atelectasis), trouble breathing (acute respiratory distress syndrome), and worsening of asthma.
- **blood clots.** GONAL-F RFF may increase your chance of having blood clots in your blood vessels. Blood clots can cause:
 - blood vessel problems (thrombophlebitis)
 - stroke
 - loss of your arm or leg
 - blood clot in your lung (pulmonary embolus)
 - heart attack
- **twisting (torsion) of your ovary.** GONAL-F RFF may increase the chance of your ovary twisting if you already have certain conditions such as OHSS, pregnancy and previous abdominal surgery. Twisting of your ovary may lead to blood flow being cut off to your ovary.
- **ovaries that are too large.** GONAL-F RFF may cause your ovaries to be abnormally large. Symptoms of large ovaries include bloating or pain in your lower stomach (pelvic) area.
- **pregnancy with and birth of multiple babies.** GONAL-F RFF may increase your chance of having a pregnancy with more than 1 baby. Having a pregnancy and giving birth to more than 1 baby at a

time increases the health risk for you and your babies. Your healthcare provider should tell you about your chances of multiple births.

- **birth defects.** A baby born after an ART cycle may have an increased chance of having birth defects. Your chances of having a baby with birth defects may increase depending on:
 - your age
 - certain sperm problems
 - your genetic background and that of your partner
 - a pregnancy with more than 1 baby at a time
- **ectopic pregnancy (pregnancy outside your womb).** GONAL-F RFF may increase your chance of having a pregnancy that is abnormally outside of your womb. Your chance of having a pregnancy outside of your womb is increased if you also have fallopian tube problems. Call your healthcare provider right away if you have symptoms of an ectopic pregnancy including:
 - stomach or pelvic pain especially on one side
 - neck pain
 - nausea and vomiting
 - shoulder pain
 - rectal pain
- **miscarriage.** Your chance of loss of an early pregnancy may be increased if you had difficulty becoming pregnant.
- **tumors of the ovary.** If you have used medicines like GONAL-F RFF more than 1 time to get pregnant, you may have an increased chance of having tumors in your ovary(ies) (including cancer).

Common side effects of GONAL-F RFF include:

- | | | |
|------------|---|--------------------|
| • headache | • stomach pain | • stomach bloating |
| • OHSS | • swelling and pain at the injection site | • diarrhea |
| • nausea | • gas | • ovarian cyst |

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of GONAL-F RFF. For more information, call your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GONAL-F RFF?

- Before you use GONAL-F RFF for the first time, store your vials:
 - in the refrigerator between 36°F to 46°F (2°C to 8°C) until the expiration date, or
 - store your vials at room temperature between 68°F to 77°F (20°C to 25°C) until the expiration date.
- After you use GONAL-F RFF throw away (discard) unused material.
- Store your GONAL-F RFF vials in a safe place.
- Store GONAL-F RFF away from light.

Keep GONAL-F RFF and all medicines out of the reach of children.

General Information about the safe and effective use of GONAL-F RFF.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use GONAL-F RFF for a condition for which it was not prescribed. Do not give GONAL-F RFF to other people, even if they have the same condition that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about GONAL-F RFF that is written for health professionals.

For more information, go to www.fertilitylifelines.com, or call 1-866-538-7879.

What are the ingredients in GONAL-F RFF?

Active ingredient: follitropin alfa (r-hFSH)

Inactive ingredients: dibasic sodium phosphate dihydrate, methionine, monobasic sodium phosphate dihydrate, phosphoric acid and or sodium hydroxide, polysorbate 20, sucrose

Instructions for Use
GONAL-F® RFF
(follitropin alfa injection)
for subcutaneous use



Important

- **Read these instructions completely before you begin.**
- GONAL-F RFF is for use under the skin only (subcutaneous).
- Only use GONAL-F RFF if your healthcare provider trains you on how to use it correctly.

Warning:

- **Do not** reuse needles.
- **Do not** share your GONAL-F RFF needles or syringes with another person. You may get a serious infection from other people or other people may get a serious infection from you.
- The syringes and needles that come with your GONAL-F RFF are meant for use with GONAL-F RFF only. **Do not** use GONAL-F RFF syringes to inject other medicines or hormones.
- **The GONAL-F® RFF vial comes in only 75 International Units (IU)**

Supplies needed to give your GONAL-F RFF injection.

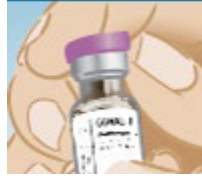
- a clean flat surface like a table
- 1 GONAL-F RFF 75 IU vial
- 1 Prefilled Syringe of Sterile Water for Injection, USP
- (1) 18 G 1½" Mixing Needle
- (1) 29 G ½" Injection Needle
- 1 FDA-cleared sharps container
- 2 alcohol pads
- 1 gauze or cotton ball

Gather your supplies.

- Prepare a clean, flat surface, such as a table or countertop, in a well-lit area.

Step 1 Mixing (reconstituting)

- Wash your hands with soap and water.
- Using your thumb, flip off the plastic cap of the GONAL-F RFF vial.



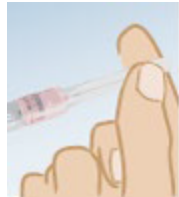
- Wipe the top of the vial stopper with an alcohol swab.



- Carefully twist and pull off the protective cap of the prefilled syringe of Sterile Water. Do not touch the needle or allow it to touch any surface.



- Remove the safety seal cover of the 18 G 1 ½ " pink needle. Twist the needle onto the prefilled syringe until it is tightened, being careful to keep the protective needle cap in place. Carefully remove the protective needle cap. Do not touch or allow the needle to touch any surface.



- Hold the GONAL-F RFF vial firmly on a flat surface.
- Position the prefilled syringe of Sterile Water in a straight, upright position over the marked center circle of the rubber stopper on the vial of the GONAL-F RFF powder.
- Insert the needle through the center circle of the rubber stopper on the vial of the GONAL-F RFF powder while keeping it in a straight, upright position.



- Slowly inject the Sterile Water into the vial of GONAL-F RFF powder by pressing down on the syringe plunger.



- Gently, rotate the vial between your fingers until the powder is dissolved. **Do not** shake.
- While keeping the needle in the vial of GONAL-F RFF, lift and turn the vial upside down.
- With the needle tip in the liquid, slowly pull back the 18 G 1 ½ " pink needle as far as needed until you withdraw the entire contents of the vial. Remove the needle from the vial.



- Gently pull the plunger back to allow a small air space. Recap the needle.
- Twist off the 18 G 1 ½ " pink needle from the syringe and immediately throw away (dispose of) the needle in an FDA-cleared sharps disposal container (See Step 4: How to throw away used needles and syringes) unless you need to mix more vials to get your prescribed dose.
- **Do not** use this needle to give your injection.



Note: If your dose requires more than 1 vial of GONAL-F RFF 75 IU, use the same 18 G 1 ½ " pink needle and syringe containing the mixture to mix (reconstitute) additional vials. Follow Step 1.

Step 2 Preparing the dose

- Check that the GONAL-F RFF liquid solution is clear. Do not use if the liquid is discolored or contains any particles. If this happens, throw it away and call your healthcare provider or pharmacist right away.



- Allow the liquid solution to come to room temperature before giving your injection.

Caution: Do not use a microwave or other heating element to warm up the reconstituted liquid.

- Remove the safety seal cover of the 29 G 1 ½ " red needle. Twist the needle onto the prefilled syringe until it is tightened, being careful to keep the protective needle cap in place. Carefully remove the protective needle cap. Do not touch or allow the needle to touch any surface
- With the syringe pointing upward, gently tap on the syringe and slowly push the plunger until all air bubbles are gone and a drop of liquid appears on the tip of the needle.



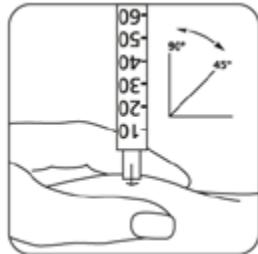
- Recap the needle and set on a clean, flat surface. The syringe is now ready for giving your prescribed dose of GONAL-F RFF.

Step 3 Injecting the dose

- Your healthcare provider should show you how to set the prescribed dose and use the syringe.
- Change your injection site each day to decrease discomfort. GONAL-F RFF is injected under the skin (subcutaneously) of your stomach area, upper arm, or upper leg.



- Uncap the syringe and inject the dose as directed by your healthcare provider.



- Lightly press a cotton ball or gauze on the site if needed.

Step 4 How to throw away used needles and syringes

- Put used needles and syringes in an FDA-cleared sharps disposal container immediately after use.



Warning: Do not throw away loose needles and pens in your household trash.

- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
 - Made of heavy-duty plastic,
 - Can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - Upright and stable during use,
 - Leak resistant, and
 - Properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>
 - **Do not** reuse the needles
 - **Do not** throw away (dispose of) your used sharps disposal container in your household trash unless your community guidelines permit this.
 - **Do not** recycle your used sharps disposal container.

For more information, go to <http://www.fda.gov/safesharpsdisposal>.

Step 5 How to store your GONAL-F RFF vials

- Store all vials of GONAL-F® RFF powder away from light.
- Store the powder vials in the refrigerator between 36° F and 46° F (2°C and 8° C) until the expiration date, or at room temperature between 68° F and 77° F (20°C and 25°C) until the expiration date.
- **Keep the GONAL-F RFF vials and all medicines out of the reach of children.**

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EMD Serono, Inc. is an affiliate of Merck: KGaA, Darmstadt, Germany

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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