

1 **Gonal-f® RFF** (follitropin alfa for injection)

2 **For subcutaneous injection**

3 *revised formulation female

4 **DESCRIPTION**

DRUGS-ABOUT.COM

5 Gonal-f® RFF (follitropin alfa for injection) is a human follicle stimulating hormone (FSH)
6 preparation of recombinant DNA origin, which consists of two non-covalently linked, non-
7 identical glycoproteins designated as the α - and β -subunits. The α - and β -subunits have 92
8 and 111 amino acids, respectively, and their primary and tertiary structure are
9 indistinguishable from those of human follicle stimulating hormone. Recombinant FSH
10 production occurs in genetically modified Chinese Hamster Ovary (CHO) cells cultured in
11 bioreactors. Purification by immunochromatography using an antibody specifically binding
12 FSH results in a highly purified preparation with a consistent FSH isoform profile, and a high
13 specific activity. The biological activity of follitropin alfa is determined by measuring the
14 increase in ovary weight in female rats. The in vivo biological activity of follitropin alfa has
15 been calibrated against the first International Standard for recombinant human follicle
16 stimulating hormone established in 1995 by the Expert Committee on Biological Standards
17 of the World Health Organization. Gonal-f® RFF contains no luteinizing hormone (LH)
18 activity. Based on available data derived from physico-chemical tests and bioassays,
19 follitropin alfa and follitropin beta, another recombinant follicle stimulating hormone
20 product, are indistinguishable.

21 Gonal-f® RFF is a sterile, lyophilized powder intended for subcutaneous injection after
22 reconstitution.

23 Each Gonal-f® RFF single-dose vial is filled with 82 IU (6 μ g) follitropin alfa to deliver 75
24 IU (5.5 μ g) follitropin alfa and contains 30 mg sucrose, 1.11 mg dibasic sodium phosphate
25 dihydrate, 0.45 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, and 0.05
26 mg polysorbate 20. Phosphoric acid and/or sodium hydroxide may be used prior to
27 lyophilization for pH adjustment. Vials are reconstituted with Sterile Water for Injection,
28 USP.

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

31 Therapeutic Class: Infertility

32 CLINICAL PHARMACOLOGY

33 Gonal-f® RFF (follitropin alfa for injection) stimulates ovarian follicular growth in women
34 who do not have primary ovarian failure. FSH, the active component of Gonal-f® RFF is the
35 primary hormone responsible for follicular recruitment and development. In order to effect
36 final maturation of the follicle and ovulation in the absence of an endogenous LH surge,
37 human chorionic gonadotropin (hCG) must be given following the administration of Gonal-
38 f® RFF when monitoring of the patient indicates that sufficient follicular development has
39 occurred. There is interpatient variability in response to FSH administration.

40 Pharmacokinetics

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

44 The descriptive statistics for the pharmacokinetic parameters are presented in Table 1.

45 **Table 1: Pharmacokinetic parameters of FSH following administration of Gonal-f®**
46 **RFF**

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%

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

49 Absorption

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

53 Distribution

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

55 Metabolism/Excretion

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

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

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

62 **Clinical Studies:**

63 The safety and efficacy of Gonal-f® RFF have been examined in two clinical studies: one
64 study (Study 22240) for ovulation induction and one study (Study 21884) for assisted
65 reproductive technologies (ART).

66 1. Ovulation Induction (OI):

67 Study 22240 was a phase III, assessor-blind, randomized, comparative, multinational,
68 multicenter study in oligo-anovulatory infertile women undergoing ovulation induction.
69 Patients were randomized to either Gonal-f® RFF (n=83), administered subcutaneously, or a
70 comparator recombinant human FSH. The use of insulin-sensitizing agents was allowed
71 during the study. Efficacy was assessed using the mean ovulation rate in the first cycle of
72 treatment. The cycle 1 ovulation rate (primary outcome) for Gonal-f® RFF is presented in
73 Table 2. Additionally, this table includes cumulative secondary outcome results from cycle 1
74 through 3. Study 22240 was not powered to demonstrate differences in these secondary
75 outcomes.

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

Study 22240	Gonal-f® RFF (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
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- 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.

85 2. Assisted Reproductive Technologies (ART):

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

97 **Table 3: Treatment Outcomes in ART**

Study 21884	Gonal-f® RFF 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

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- 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

104 **INDICATIONS AND USAGE**

105 Gonal-f® RFF (follitropin alfa for injection) is indicated for the induction of ovulation and
106 pregnancy in the oligo-anovulatory infertile patient in whom the cause of infertility is

107 functional and not due to primary ovarian failure. Gonal-f® RFF is also indicated for the
108 development of multiple follicles in the ovulatory patient participating in an Assisted
109 Reproductive Technology (ART) program.

110 **Selection of Patients:**

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

122 **CONTRAINDICATIONS**

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

- 124 1. Prior hypersensitivity to recombinant FSH preparations or one of their excipients.
- 125 2. High levels of FSH indicating primary gonadal failure.
- 126 3. Uncontrolled thyroid or adrenal dysfunction.
- 127 4. Sex hormone dependent tumors of the reproductive tract and accessory organs.
- 128 5. An organic intracranial lesion such as a pituitary tumor.
- 129 6. Abnormal uterine bleeding of undetermined origin (see "Selection of Patients").
- 130 7. Ovarian cyst or enlargement of undetermined origin (see "Selection of Patients").
- 131 8. Pregnancy.

132 **WARNINGS**

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

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

142 **Overstimulation of the Ovary During FSH Therapy:**

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

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

151 Ovarian Hyperstimulation Syndrome (OHSS): OHSS is a medical event distinct from
152 uncomplicated ovarian enlargement. Severe OHSS may progress rapidly (within 24 hours to
153 several days) to become a serious medical event. It is characterized by an apparent dramatic
154 increase in vascular permeability which can result in a rapid accumulation of fluid in the
155 peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of
156 development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. The
157 following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal
158 distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe
159 ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal
160 hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural
161 effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see
162 "Pulmonary and Vascular Complications"). Transient liver function test abnormalities
163 suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on

164 liver biopsy, have been reported in association with Ovarian Hyperstimulation Syndrome
165 (OHSS).

166 OHSS occurred in 6 of 83 (7.2%) Gonal-f® RFF treated women in Study 22240 (ovulation
167 induction); none were classified as severe. In Study 21884 (ART), OHSS occurred in 11 of
168 237 (4.6%) Gonal-f® RFF treated women and 1 (0.42%) was classified as severe. OHSS
169 may be more severe and more protracted if pregnancy occurs. OHSS develops rapidly;
170 therefore, patients should be followed for at least two weeks after hCG administration. Most
171 often, OHSS occurs after treatment has been discontinued and reaches its maximum at about
172 seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset
173 of menses. If there is evidence that OHSS may be developing prior to hCG administration
174 (see "Precautions / Laboratory Tests"), the hCG must be withheld.

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

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

178 **Pulmonary and Vascular Complications:**

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

187 **Multiple Births:** Reports of multiple births have been associated with Gonal-f® RFF
188 treatment. In Study 22240 for women receiving Gonal-f® RFF over three treatment cycles,
189 20% of live births were multiple births. In Study 21884, 35.1% of live births were multiple
190 births in women receiving Gonal-f® RFF. The rate of multiple births is dependent on the
191 number of embryos transferred. The patient should be advised of the potential risk of
192 multiple births before starting treatment.

193 **PRECAUTIONS**

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

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

201 See "DOSAGE AND ADMINISTRATION" for "PATIENT INSTRUCTIONS FOR USE
202 OF GONAL-F® RFF".

203 **Laboratory Tests:** In most instances, treatment of women with Gonal-f® RFF results only
204 in follicular recruitment and development. In the absence of an endogenous LH surge, hCG
205 is given when monitoring of the patient indicates that sufficient follicular development has
206 occurred. This may be estimated by ultrasound alone or in combination with measurement of
207 serum estradiol levels. The combination of both ultrasound and serum estradiol
208 measurement are useful for monitoring the development of follicles, for timing of the
209 ovulatory trigger, as well as for detecting ovarian enlargement and minimizing the risk of the
210 Ovarian Hyperstimulation Syndrome and multiple gestation. It is recommended that the
211 number of growing follicles be confirmed using ultrasonography because plasma estrogens
212 do not give an indication of the size or number of follicles.

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

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

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

- 222 1. Fluid in the cul-de-sac;

- 223 2. Ovarian stigmata;
224 3. Collapsed follicle; and
225 4. Secretory endometrium.

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

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

229 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have
230 not been performed to evaluate the carcinogenic potential of Gonal-f® RFF. However,
231 follitropin alfa showed no mutagenic activity in a series of tests performed to evaluate its
232 potential genetic toxicity including, bacterial and mammalian cell mutation tests, a
233 chromosomal aberration test and a micronucleus test.

234 Impaired fertility has been reported in rats, exposed to pharmacological doses of follitropin
235 alfa (≥ 40 IU/kg/day) for extended periods, through reduced fecundity.

236 **Pregnancy:** Pregnancy Category X. See CONTRAINDICATIONS.

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

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

243 **ADVERSE REACTIONS**

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

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

248 Table 4: **Safety Profile in Ovulation Induction Study 22240**

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Body System Preferred Term	Gonal-f® RFF 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%)

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

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

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

255 Table 5: **Safety Profile in Assisted Reproductive Technologies Study 21884**

Body System Preferred Term	Gonal-f® RFF Patients (%) Experiencing Events n=237†
Gastro-intestinal System	

Body System Preferred Term	Gonal-f® RFF Patients (%) Experiencing Events n=237[†]
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%)

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[†] total patients treated with Gonal-f® RFF

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

259 The following medical events have been reported subsequent to pregnancies resulting from
260 Gonal-f® RFF therapy in controlled clinical studies:

- 261 1. Spontaneous Abortion
- 262 2. Ectopic Pregnancy
- 263 3. Premature Labor
- 264 4. Postpartum Fever

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

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

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

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

276 **Post Marketing Reports**

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

279 **OVERDOSAGE**

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

283 **DOSAGE AND ADMINISTRATION**

284 Each Gonal-f® RFF Single-Dose vial delivers 75 IU follitropin alfa, respectively.

285 **Dosage:**

286 **Infertile Patients with oligo-anovulation:** The dose of Gonal-f® RFF (follitropin alfa for
287 injection) to stimulate development of the follicle must be individualized for each patient.

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

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

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

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

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

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

338 **Administration:**

339 Dissolve the contents of one or more single-dose vials of Gonal-f® RFF in 1.0 mL of Sterile
340 Water for Injection, USP (concentration should not exceed 450 IU/mL) and ADMINISTER
341 SUBCUTANEOUSLY immediately. Any unused reconstituted material should be
342 discarded.

343 **PATIENT INSTRUCTIONS FOR USE FOR GONAL-F® RFF**

344 **Step 1: Mixing (reconstituting) the vial containing Gonal-f® RFF**

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346 1. Wash your hands with soap and water.

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348 2. Prepare a clean, flat surface for mixing your
349 Gonal-f® RFF vials. Place alcohol wipes on the
350 surface within easy reach.

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354 3. Using your thumb, flip off the plastic cap of the
355 Gonal-f® RFF vial(s).

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357 4. Wipe the top of the vial stopper with an alcohol
358 wipe.

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360 5. Remove the wrapping from the 18G 1-1/2” pink
361 mixing needle.

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363 6. Carefully remove the protective cap off the pre-
364 filled syringe labeled “sterile water for injection,
365 USP”. Twist the mixing needle on the prefilled
366 syringe until it is tightened and remove the
367 needle cap.

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369 7. Position the 18G 1-1/2” needle of the syringe of
370 water in a straight, upright position over the
371 marked center circle of the rubber stopper on the
372 vial of Gonal-f® RFF powder. Keep the 18G 1-
373 1/2” needle at a 90 degree angle to the rubber
374 stopper as you insert it through the center circle,
375 or it may be difficult to depress the plunger.
376 Slowly inject the water into the vial by
377 depressing the syringe plunger.

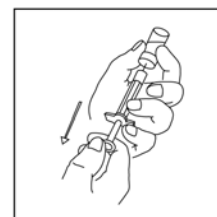
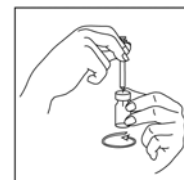
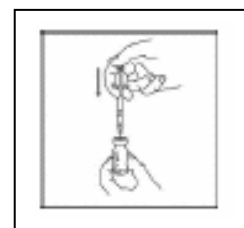
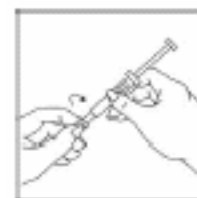
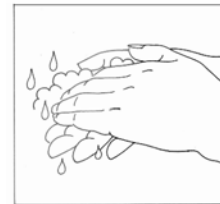
378

379 8. Leave the 18G 1-1/2” needle and syringe in the
380 vial. Gently rotate the vial between your fingers
381 until the powder is dissolved. Do not shake the
382 vial. If bubbles appear, wait a few moments for
383 the bubbles to settle. The liquid drug should be
384 clear.

385

386 9. Draw the total contents of the vial into the
387 syringe. If necessary, invert the vial and pull
388 back the 18G 1-1/2” needle as far as needed to
389 withdraw the entire contents of the vial.
390 Remove the 18G 1-1/2” needle and syringe
391 containing the solution from the vial.

392



- 393 10. If more than one vial of powder medication is to
394 be dissolved repeat steps 3, 4 and 7 to 9. A new
395 alcohol wipe should be used to clean each vial.
396 Use the same 18G 1-1/2" needle and syringe
397 now containing reconstituted solution to
398 reconstitute the additional vial(s). (Discard any
399 other unused syringes of water for injection.)
400
- 401 11. Gently pull the plunger back to allow a small air
402 space. Carefully recap the needle. Twist off the
403 mixing needle from the syringe and discard
404 safely.
405

406 **Step 2: Determining your dose on the injection**
407 **syringe**

408 Your doctor will instruct you to take a specific dose of
409 Gonal-f® RFF.
410

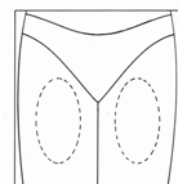
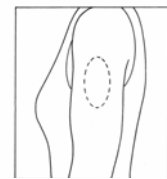
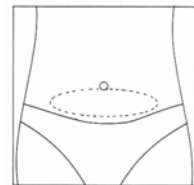
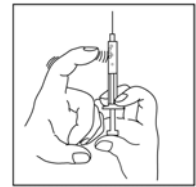
411 **Step 3: Preparing your dose**
412

- 413 12. Remove the wrapping from the 29G ½" red
414 injection needle. Twist the injection needle on
415 the syringe and remove the need cap.
416
- 417 13. Invert the syringe with the 29G ½" needle for
418 injection facing up toward the ceiling, gently tap
419 the syringe, and push the plunger until all air
420 bubbles have been expelled. This step may
421 need to be repeated if all air bubbles are not
422 expelled. Slightly depress the plunger until a
423 drop of liquid is release from the tip of the
424 needle.
425
- 426 14. Recap the 29G ½" needle for injection while
427 preparing the injection site. Carefully lay the
428 syringe on a flat, clean surface. Do not touch
429 the needle or allow the needle to touch any
430 surface.
431

432 You should now be ready to prepare to receive the
433 injection.
434

435 **Step 4: Injecting your dose**

436 Your doctor, nurse, or pharmacist should provide you
437 with injection training. Inject the prescribed dose as
438 directed. Usual injection sites include the skin on the
439 stomach, upper arm, or upper leg. Change the injection
440 location each day to minimize discomfort.
441



442 15. All needles should be disposed of in an
443 appropriate needle disposal container as
444 directed by the doctor.
445

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

449 **HOW SUPPLIED**

450 Gonal-f® RFF (follitropin alfa for injection) is supplied in a sterile, lyophilized form in
451 single-dose vials containing 82 IU with diluent (Sterile Water for Injection, USP) in a pre-
452 filled syringe. Following reconstitution with the diluent as described, upon administration
453 each vial will deliver a dose of 75 IU.

454 Lyophilized vials may be stored refrigerated or at room temperature (2°-25°C/36°-77°F).
455 Protect from light. Use immediately after reconstitution. Discard unused material.

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

458 Note: No antimicrobial or other substance has been added to the Sterile Water for Injection
459 for the Single-Dose Vials. Sterile Water for Injection is not suitable for intravascular
460 injection without its first having been made approximately isotonic by the addition of a
461 suitable solute.

462 The following package combinations are available:

463 1 vial Gonal-f® RFF 75 IU and 1 pre-filled syringe Sterile Water for Injection, USP, 1 mL, 1
464 reconstitution needle (18 gauge), 1 administration needle (29 gauge), NDC 44087-9005-1

465 10 vials Gonal-f® RFF 75 IU and 10 pre-filled syringes Sterile Water for Injection, USP, 1
466 mL, 10 reconstitution needle (18 gauge), 10 administration needle (29 gauge), NDC 44087-
467 9005-6

468 *Rx only*

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469 Manufactured for: SERONO, INC., Rockland, MA 02370 U.S.A.

470 Revised: December 2006