

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-765

APPROVED LABELING

1 **Tradename** (follitropin alfa for injection)

2 **For subcutaneous injection**

3

4 **DESCRIPTION**

5 Tradename (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. Tradename 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 Tradename is a sterile, lyophilized powder intended for subcutaneous injection after
22 reconstitution.

23 Each Tradename single-dose vial is filled with 41 IU (3 μ g), 82 IU (6 μ g), or 165 IU (12 μ g)
24 follitropin alfa to deliver 37.5 IU (2.8 μ g), 75 IU (5.5 μ g), or 150 IU (11 μ g) follitropin alfa,
25 respectively, and contains 30 mg sucrose, 1.11 mg dibasic sodium phosphate dihydrate, 0.45
26 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, and 0.05 mg polysorbate
27 20. O-phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH
28 adjustment. Vials are reconstituted with Sterile Water for Injection, USP.

29 Under current storage conditions, Tradename may contain up to 10% of oxidized follitropin
30 alfa.

31 Therapeutic Class: Infertility

32 CLINICAL PHARMACOLOGY

33 Tradename (follitropin alfa for injection) stimulates ovarian follicular growth in women who
34 do not have primary ovarian failure. FSH, the active component of Tradename is the primary
35 hormone responsible for follicular recruitment and development. In order to effect final
36 maturation of the follicle and ovulation in the absence of an endogenous LH surge, human
37 chorionic gonadotropin (hCG) must be given following the administration of Tradename
38 when monitoring of the patient indicates that sufficient follicular development has occurred.
39 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 Tradename to 21 pre-menopausal healthy female volunteers who
43 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 (mean \pm SD) of FSH following administration**
46 **of Tradename**

Population	Healthy Volunteers (n=21)	
Dose (IU)	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 Tradename following subcutaneous administration is slower than the
51 elimination rate. Hence, the pharmacokinetics of Tradename are absorption rate-limited.

52 Distribution

53 Human tissue or organ distribution of FSH has not been determined for Tradename.

54 Metabolism/Excretion55 FSH metabolism and excretion following administration of Tradename have not been studied
56 in humans.57 **Special populations:** Safety, efficacy, and pharmacokinetics of Tradename in patients with
58 renal or hepatic insufficiency have not been established.59 **Drug-Drug Interactions:** No drug-drug interaction studies have been conducted (see
60 PRECAUTIONS).61 **Clinical Studies:**62 The safety and efficacy of Tradename have been examined in two clinical studies: one study
63 (Study 22240) for ovulation induction and one study (Study 21884) for assisted reproductive
64 technologies (ART).65 1. Ovulation Induction (OI):66 Study 22240 was a phase III, assessor-blind, randomized, comparative, multinational,
67 multicenter study in oligo-anovulatory infertile women undergoing ovulation induction.
68 Patients were randomized to either Tradename (n=83), administered subcutaneously, or a
69 comparator recombinant human FSH. The use of insulin-sensitizing agents was allowed
70 during the study. Efficacy was assessed using the mean ovulation rate in the first cycle of
71 treatment. The cycle 1 ovulation rate (primary outcome) for Tradename is presented in Table72 2. Additionally, this table includes cumulative secondary outcome results from cycle 1
73 through 3. Study 22240 was not powered to demonstrate differences in these secondary
74 outcomes.75 **Table 2: Cumulative Ovulation and Clinical Pregnancy Rates in Ovulation Induction**

Study 22240	Tradename (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.

84 2. Assisted Reproductive Technologies (ART):

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

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

Study 21884	Tradename 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

- 99 c A clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heart activity) was visualized
100 by ultrasound on day 35-42 after hCG administration.
101 d Secondary efficacy parameter. Study 21884 was not powered to demonstrate differences in this parameter

102 INDICATIONS AND USAGE

103 Tradename (follitropin alfa for injection) is indicated for the induction of ovulation and
104 pregnancy in the oligo-anovulatory infertile patient in whom the cause of infertility is
105 functional and not due to primary ovarian failure. Tradename is also indicated for the
106 development of multiple follicles in the ovulatory patient participating in an Assisted
107 Reproductive Technology (ART) program.

108 Selection of Patients:

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

120 CONTRAINDICATIONS

121 Tradename (follitropin alfa for injection) is contraindicated in women who exhibit:

- 122 1. Prior hypersensitivity to recombinant FSH preparations or one of their excipients.
- 123 2. High levels of FSH indicating primary gonadal failure.
- 124 3. Uncontrolled thyroid or adrenal dysfunction.
- 125 4. Sex hormone dependent tumors of the reproductive tract and accessory organs.

- 126 5. An organic intracranial lesion such as a pituitary tumor.
- 127 6. Abnormal uterine bleeding of undetermined origin (see "Selection of Patients").
- 128 7. Ovarian cyst or enlargement of undetermined origin (see "Selection of Patients").
- 129 8. Pregnancy.

130 **WARNINGS**

131 Tradename (follitropin alfa for injection) should only be used by physicians who are
132 thoroughly familiar with infertility problems and their management.

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

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

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

146 If the ovaries are abnormally enlarged on the last day of Tradename therapy, hCG should not
147 be administered in this course of therapy. This will reduce the chances of development of
148 Ovarian Hyperstimulation Syndrome.

149 Ovarian Hyperstimulation Syndrome (OHSS): OHSS is a medical event distinct from
150 uncomplicated ovarian enlargement. Severe OHSS may progress rapidly (within 24 hours to
151 several days) to become a serious medical event. It is characterized by an apparent dramatic
152 increase in vascular permeability which can result in a rapid accumulation of fluid in the

153 peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of
154 development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. The
155 following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal
156 distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe
157 ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal
158 hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural
159 effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see
160 "Pulmonary and Vascular Complications"). Transient liver function test abnormalities
161 suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on
162 liver biopsy, have been reported in association with Ovarian Hyperstimulation Syndrome
163 (OHSS).

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

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

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

176 **Pulmonary and Vascular Complications:**

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

183 resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic
184 events have resulted in death.

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

191 PRECAUTIONS

192 **General:** Careful attention should be given to the diagnosis of infertility in candidates for
193 Tradename (follitropin alfa for injection) therapy (see "Indications and Usage/ Selection of
194 Patients").

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

199 A 'Patient's Information Leaflet' is provided for patients prescribed Tradename.

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

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

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

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

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

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

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

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

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

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

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

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

240 ADVERSE REACTIONS

241 The safety of Tradename was examined in two clinical studies [(one ovulation induction
 242 study (n=83) and one study in ART (n=237)].

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

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

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Body System Preferred Term	Tradename 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%)

Body System Preferred Term	Tradename Patients (%) Experiencing Events Treatment cycles = 176* n=83†
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 Tradename

249 Headache occurred in greater than 20% of patients receiving Tradename in this study.

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

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

Body System Preferred Term	Tradename Patients (%) Experiencing Events n=237†
Gastro-intestinal System	
Abdominal Pain	55 (23.2%)
Nausea	19 (8.0%)
Body as a Whole- General	
Abdomen Enlarged	33 (13.9%)
Pain	7 (3.0%)
Central and Peripheral Nervous System	
Headache	44 (18.6%)
Dizziness	5 (2.1%)
Application Site Disorders	
Injection site bruising	23 (9.7%)
Injection site pain	13 (5.5%)
Injection site inflammation	10 (4.2%)
Injection site reaction	10 (4.2%)
Application site oedema	6 (2.5%)
Reproductive, Female	
Ovarian Hyperstimulation	11 (4.6%)
Intermenstrual Bleeding	9 (3.8%)

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† total patients treated with Tradename

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

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

258 1. Spontaneous Abortion

259 2. Ectopic Pregnancy

260 3. Premature Labor

261 4. Postpartum Fever

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

264 The following adverse reactions have been previously reported during Tradename therapy:

265 1. Pulmonary and vascular complications (see "Warnings"),

266 2. Adnexal torsion (as a complication of ovarian enlargement),

267 3. Mild to moderate ovarian enlargement,

268 4. Hemoperitoneum

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

272 **Post Marketing Reports**

273 During post-market surveillance, reports of hypersensitivity reactions including
274 anaphylactoid reactions have been reported with the use of Tradename.

275 **OVERDOSAGE**

276 Aside from possible ovarian hyperstimulation and multiple gestations (see "Warnings"),
277 there is no information on the consequences of acute overdosage with Tradename (follitropin
278 alfa for injection).

279 **DOSAGE AND ADMINISTRATION**

280 Each Tradename Single-Dose vial delivers 37.5 IU, 75 IU, and 150 IU follitropin alfa,
281 respectively.

282 **Dosage:**

283 **Infertile Patients with oligo-anovulation:** The dose of Tradename (follitropin alfa for
284 injection) to stimulate development of the follicle must be individualized for each patient.

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

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

304 The initial dose administered in the subsequent cycles should be individualized for each
305 patient based on her response in the preceding cycle. Doses larger than 300 IU of FSH per
306 day are not routinely recommended. As in the initial cycle, hCG must be given after the last
307 dose of Tradename to complete follicular development and induce ovulation. The

308 precautions described above should be followed to minimize the chance of development of
309 the Ovarian Hyperstimulation Syndrome.

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

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

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

335 **Administration:**

336 Dissolve the contents of one or more single-dose vials of Tradename (37.5 IU, 75 IU or 150
337 IU) in 0.5-1.0 mL of Sterile Water for Injection, USP (concentration should not exceed 225

338 IU/0.5 mL) and ADMINISTER SUBCUTANEOUSLY immediately. Any unused
339 reconstituted material should be discarded.

340 Patient Instructions for Use for Tradename

341 Step 1: Mixing (reconstituting) the vial containing Tradename

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1. Wash your hands with soap and water.

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2. Prepare a clean, flat surface for mixing your Tradename vials. Place alcohol wipes on the surface within easy reach.

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3. Using your thumb, flip off the plastic cap of the Tradename vial(s).

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

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5. Holding the "barrel" of the pre-filled syringe labeled 'Sterile Water for Injection, USP', twist and pull off the protective cap and the inner rubber cap.

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6. Push the 18 gauge (G) 1-1/2 inch (") needle on the pre-filled syringe until it is tightened. Holding the hub or base of the needle, secure the needle on the tip of the prefilled syringe and remove the needle cap.

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7. Position the 18G 1-1/2" needle of the syringe of water in a straight, upright position over the marked center circle of the rubber stopper on the vial of Tradename powder. Keep the 18G 1-1/2" needle at a 90 degree angle to the rubber stopper as you insert it through the center circle, or it may be difficult to depress the plunger. Slowly inject the water into the vial by depressing the syringe plunger.

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

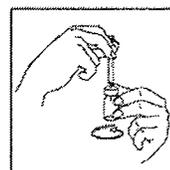
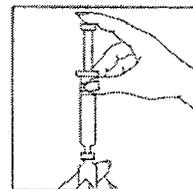
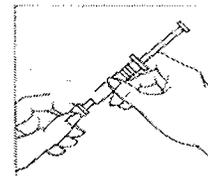
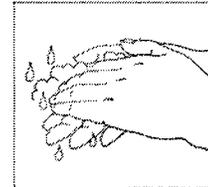
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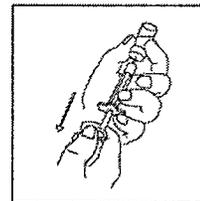
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9. Draw the total contents of the vial into the syringe. If necessary, invert the vial and pull back the 18G 1-1/2" needle as far as needed to withdraw the entire contents of the vial. Remove the 18G 1-1/2" needle and syringe containing the solution from the vial.
10. If more than one vial of powder medication is to be dissolved repeat steps 3, 4 and 7 to 9. A new alcohol wipe should be used to clean each vial. Use the same 18G 1-1/2" needle and syringe now containing reconstituted solution to reconstitute the additional vial(s). (Discard any other unused syringes of water for injection.)
11. Gently pull the plunger back to allow a small air space. Carefully recap the needle. Twist and pull off the 18G 1-1/2" needle from the syringe and discard safely.

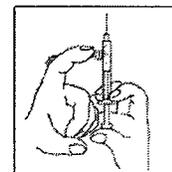


Step 2: Determining your dose on the injection syringe

Your doctor will instruct you to take a specific dose of Tradename.

Step 3: Preparing your dose

12. Tightly push the 27G 1/2" needle for injection onto the end of the syringe. Holding the hub or base of the needle, secure the needle on the tip of the syringe. Carefully loosen and pull off the protective cap from the needle.
13. Invert the syringe with the 27G 1/2" needle for injection facing up toward the ceiling, gently tap the syringe, and push the plunger until all air bubbles have been expelled. This step may need to be repeated if all air bubbles are not expelled. Slightly depress the plunger until a drop of liquid is released from the tip of the needle.
14. Recap the 27G 1/2" needle for injection while preparing the injection site. Carefully lay the syringe on a flat, clean surface. Do not touch the needle or allow the needle to touch any surface.



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

435
436 **Step 4: Injecting your dose**

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

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

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

450 **HOW SUPPLIED**

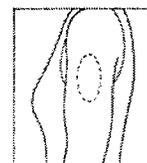
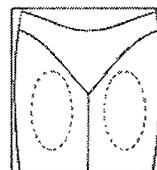
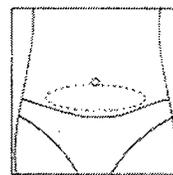
451 Tradename (follitropin alfa for injection) is supplied in a sterile, lyophilized form in single-
452 dose vials containing 41 IU, 82 IU, or 165 IU with diluent (Sterile Water for Injection, USP)
453 in a pre-filled syringe. Following reconstitution with the diluent as described, upon
454 administration each vial will deliver a dose of 37.5 IU, 75 IU, and 150 IU, respectively.

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

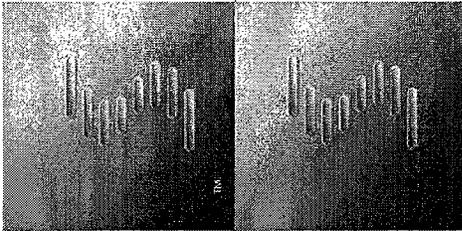
457 Sterile Water for Injection, USP is provided in a pre-filled syringe. Separate needles are
458 provided for reconstitution (18 G) and administration (27 G).

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

463 The following package combinations are available:



- 464 1 vial Tradename 37.5 IU and 1 pre-filled syringe Sterile Water for Injection, USP, 1 mL, 1
465 reconstitution needle (18 gauge), 1 administration needle (27 gauge), NDC 44087-9025-1
- 466 10 vials Tradename 37.5 IU and 10 pre-filled syringes Sterile Water for Injection, USP, 1
467 mL, 1 reconstitution needle (18 gauge), 1 administration needle (27 gauge), NDC 44087-
468 9025-6
- 469 1 vial Tradename 75 IU and 1 pre-filled syringe Sterile Water for Injection, USP, 1 mL, 1
470 reconstitution needle (18 gauge), 1 administration needle (27 gauge), NDC 44087-9005-1
- 471 10 vials Tradename 75 IU and 10 pre-filled syringes Sterile Water for Injection, USP, 1 mL,
472 1 reconstitution needle (18 gauge), 1 administration needle (27 gauge), NDC 44087-9005-6
- 473 1 vial Tradename 150 IU and 1 pre-filled syringe Sterile Water for Injection, USP, 1 mL, 1
474 reconstitution needle (18 gauge), 1 administration needle (27 gauge), NDC 44087-9010-1
- 475 10 vials Tradename 150 IU and 10 pre-filled syringes Sterile Water for Injection, USP, 1 mL,
476 1 reconstitution needle (18 gauge), 1 administration needle (27 gauge), NDC 44087-9010-6
- 477 *Rx only*
- 478 Manufactured for: SERONO, INC., Rockland, MA 02370 U.S.A.
- 479 Revised: March 2004



subcutaneous (s.c.)

Dose and Administration: See Package Insert.
Protect from light.
Use immediately after reconstitution.
Discard unused material.
Store at 2° - 25°C (36° - 77°F).

Single Dose Vial

NDC 44087-9010-1

GONAL-F[®] 150 IU
(follitropin alfa for injection)

Rx only

- 1 vial GONAL-F[®] 150 IU
- 1 pre-filled syringe Sterile Water for Injection, USP
- 1 18-gauge needle for reconstitution
- 1 27-gauge needle for administration
- For subcutaneous injection

Contents:

One vial of GONAL-F[®] contains 165 IU (12 mcg)* follitropin alfa, 30 mg sucrose, 1.11 mg dibasic sodium phosphate dihydrate, 0.45 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, 0.05 mg polysorbate 20, and phosphoric acid and/or sodium hydroxide to adjust the pH. After reconstitution with 0.5 mL to 1 mL of enclosed diluent, product will deliver at least 150 IU (11 mcg).
One pre-filled syringe of diluent, (Sterile Water for Injection, USP) containing 1 mL.
One 18-gauge needle for reconstitution. One 27-gauge needle for administration.
*Includes overfill to account for losses during administration



XXXX
XXXX
XXXX

CO-01
CED-588

GONAL-F[®] 150 IU
(follitropin alfa for injection)

Manufactured for:
Serono, Inc.
Rockland, MA 02370 USA
Made in Switzerland

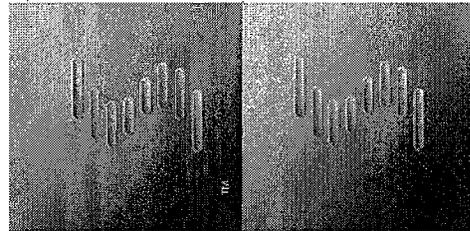


7 20303 90101 8



GONAL-F[®] 150 IU
(follitropin alfa for injection)
Lot No:
Exp. date:





subcutaneous (s.c.)

Single Dose Vial
Dose and Administration: See Package Insert.
Protect from light.
Use immediately after reconstitution.
Discard unused material.
Store at 2° - 25°C (36° - 77°F).

NDC 44087-9025-1

GONAL-[®] 37.5 IU
(follitropin alfa for injection)

Rx only

- 1 vial GONAL-[®] 37.5 IU
- 1 pre-filled syringe Sterile Water for Injection, USP
- 1 18-gauge needle for reconstitution
- 1 27-gauge needle for administration
- For subcutaneous injection



Contents:
One vial of GONAL-[®] contains 41 IU (3 mcg)* follitropin alfa, 30 mg sucrose, 1.11 mg dibasic sodium phosphate dihydrate, 0.45 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, 0.05 mg polysorbate 20, and phosphoric acid and/or sodium hydroxide to adjust the pH. After reconstitution with 0.5 mL to 1 mL of enclosed diluent, product will deliver at least 37.5 IU (2.8 mcg).
One pre-filled syringe of diluent, (Sterile Water for Injection, USP) containing 1 mL.
One 18-gauge needle for reconstitution. One 27-gauge needle for administration.
*includes overfill to account for losses during administration

USA



GONAL-[®] 37.5 IU
(follitropin alfa for injection)

Manufactured for:
Serono, Inc.
Rockland, MA 02370 USA
Made in Switzerland

COI-01
CID-586



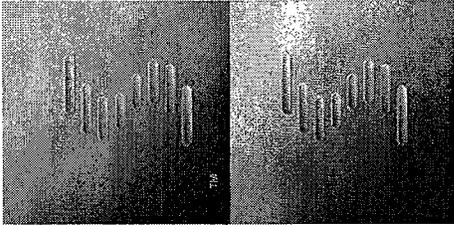
7 20303 90251 0



GONAL-[®] 37.5 IU
(follitropin alfa for injection)

Lot No:
Exp. date:





Single Dose Vial

Dose and Administration: See Package Insert.
Protect from light.
Use immediately after reconstitution.
Discard unused material.
Store at 2° - 25°C (36° - 77°F).

subcutaneous (s.c.)

NDC 44087-9005-1

GONAL-f™ 75 IU
(follitropin alfa for injection)

Rx only

- 1 vial GONAL-f®
- 1 pre-filled syringe Sterile Water for Injection, USP
- 1 18-gauge needle for reconstitution
- 1 27-gauge needle for administration
- For subcutaneous injection

Contents:

One vial of GONAL-f® contains 82 IU (6 mcg)* follitropin alfa, 30 mg sucrose, 1.11 mg dibasic sodium phosphate dihydrate, 0.45 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, 0.05 mg polysorbate 20, and phosphoric acid and/or sodium hydroxide to adjust the pH. After reconstitution with 0.5 mL to 1 mL of enclosed diluent, product will deliver at least 75 IU (5.5 mcg).

One pre-filled syringe of diluent, (Sterile Water for Injection, USP) containing 1 mL.

One 18-gauge needle for reconstitution. One 27-gauge needle for administration.

*includes overflow to account for losses during administration

Variable data

Original text	English translation	Approved by RA	Date:	Signature:
1	Lot No.:			
2	Exp. date:			
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COI-01
CED-587

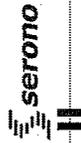
GONAL-f 75 IU
(follitropin alfa for injection)



Manufactured for:
Serono, Inc.
Rockland, MA 02370 USA
Made in Switzerland



7 20303 90051 6

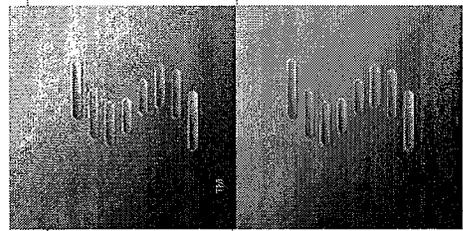


GONAL-f 75 IU
(follitropin alfa for injection)

Lot No:
Exp. date:

USA

1003



Single Dose Vial

Dose and Administration: See Package Insert.
Protect from light.
Use immediately after reconstitution.
Discard unused material.
Store at 2° - 25°C (36° - 77°F).

subcutaneous (s.c.)

NDC 44087-9005-1

GONAL-f™ 75 IU

(follitropin alfa for injection)

Rx only

- 1 vial GONAL-f®
 - 1 pre-filled syringe Sterile Water for Injection, USP
 - 1 18-gauge needle for reconstitution
 - 1 27-gauge needle for administration
- For subcutaneous injection

Contents:

One vial of GONAL-f® contains 82 IU (6 mcg)* follitropin alfa, 30 mg sucrose, 1.11 mg dibasic sodium phosphate dihydrate, 0.45 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, 0.05 mg polysorbate 20, and phosphoric acid and/or sodium hydroxide to adjust the pH. After reconstitution with 0.5 mL to 1 mL of enclosed diluent, product will deliver at least 75 IU (5.5 mcg).

One pre-filled syringe of diluent, (Sterile Water for Injection, USP) containing 1 mL.

One 18-gauge needle for reconstitution. One 27-gauge needle for administration.

*Includes overflow to account for losses during administration



Original text	English translation	Approved by RA
1 Lot No:	Date:	Signature:
2 Exp. date:		
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Variable data

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COI-01
CED-587



GONAL-f 75 IU
(follitropin alfa for injection)

Manufactured for:
Serono, Inc.
Rockland, MA 02370 USA
Made in Switzerland



7 20303 90051 6

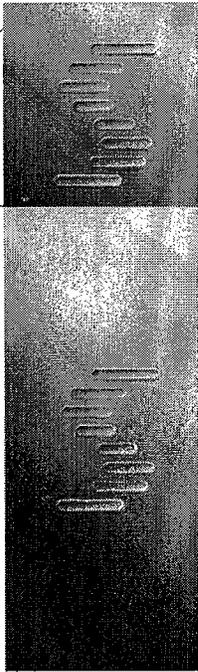
1003

USA

GONAL-f 75 IU
(follitropin alfa for injection)

Lot No:
Exp. date:





subcutaneous (s.c.)

Single Dose Vial
Dose and Administration: See Package Insert.
Protect from light.
Use immediately after reconstitution.
Discard unused material.
Store at 2° to 25°C (36° to 77°F).

NDC 44087-5005-6

GONAL- 75 IU

(follitropin alfa for injection)

Rx only

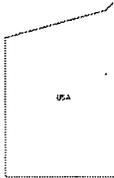
- 10 vials GONAL- *
- 10 pre-filled syringes Sterile Water for Injection, USP
- 10 18-gauge needles for reconstitution
- 10 27-gauge needles for administration
- For subcutaneous injection



Y010413
Y010412
Y010411

Variable data

Preparation	Expiry date	Lot No.
1. Lot No.	2. Exp. date	3. Lot No.
4. Lot No.	5. Exp. date	6. Lot No.



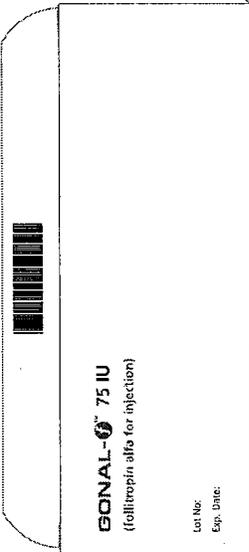
USA



Contents:
Ten vials of GONAL- * containing 92 IU (5 mcg)* follitropin alfa, 30 mg sucrose, 1.11 mg dibasic sodium phosphate dihydrate, 0.45 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, 0.05 mg polysorbate 20, and phosphoric acid and/or sodium hydroxide to adjust the pH. After reconstitution with 0.5 mL to 1 mL of enclosed diluent, product will deliver at least 75 IU (5.5 mcg).
Ten pre-filled syringes of diluent, (Sterile Water for Injection, USP) containing 1 mL.
Ten 18-gauge needles for reconstitution.
Ten 27-gauge needles for administration.

*includes overfill to account for losses during administration

CCN 06 18
C10 584

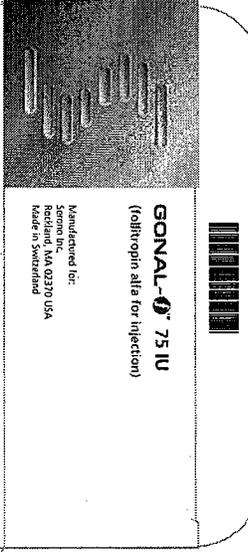


GONAL- 75 IU
(follitropin alfa for injection)

Lot No.
Exp. Date:



7 20303 50056 1



GONAL- 75 IU
(follitropin alfa for injection)

Manufactured for:
Roche Inc.
Roche Research Building
Nutley, NJ 07110 USA
Made in Switzerland



Manufactured in Sures, DC
Rockland, MA 02370 USA

GONAL-f® 150 IU
(folitropin alfa for injection)
contains 165 IU to deliver 150 IU Rx Only
Use immediately after reconstitution. Do not use red material.

Lot:
Exp.:
Code: L19XXXXX

FOR ELECTROPHORESIS INJECTION
Bioscience Resource Project
© 2004



Manufactured for Synovis, Inc.
Rochester, MA 02370 USA

GONAL-f® 37.5 IU
(hormotropin alpha for injection)
containing 41 IU to deliver 37.5 IU **Rx Only**
Use immediately after reconstitution. Discard unused material.

Lot:
Exp.:
Code: L19XXXXX

FOR SUBCUTANEOUS INJECTION
Only after reconstitution
37.5 mg/0.9 mL



Manufactured for Genovo Inc.
Tockalee, VA 02770 USA

GONAL-f® 75 IU
(follitropin alfa for injection) **Rx Only**
contains 82 IU to deliver 75 IU
Use immediately after reconstitution. Discard unused material.

Lot:
Exp.:
Code: L1970101A

FOR SIMULTANEOUS INJECTION
Insert into the package insert
for **serono**

Variable data

	Original text	English translation	Approved by RA
1	Lot:		Date:
2	Exp.:		Signature:
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4			