

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-211

APPROVED LABELING

1 **Follistim[®] AQ Cartridge (follitropin beta injection)**

2 **FOR SUBCUTANEOUS USE ONLY**

3

4 **DESCRIPTION**

5 Follistim[®] AQ Cartridge (follitropin beta injection) contains human follicle-stimulating hormone
6 (hFSH), a glycoprotein hormone which is manufactured by recombinant DNA (rDNA)
7 technology. The active drug substance, follitropin beta, has a dimeric structure containing two
8 glycoprotein subunits (alpha and beta). Both the 92 amino acid alpha-chain and the 111 amino
9 acid beta-chain have complex heterogeneous structures arising from two N-linked
10 oligosaccharide chains. Follitropin beta is synthesized in a Chinese hamster ovary (CHO) cell
11 line that has been transfected with a plasmid containing the two subunit DNA sequences
12 encoding for hFSH. The purification process results in a highly purified preparation with a
13 consistent hFSH isoform profile and high specific activity.¹ The biological activity is determined
14 by measuring the increase in ovary weight in female rats. The intrinsic luteinizing hormone
15 (LH) activity in follitropin beta is less than 1 IU per 40,000 IU FSH. The compound is
16 considered to contain no LH activity.

17 The amino acid sequence and tertiary structure of follitropin beta are indistinguishable from that
18 of human follicle-stimulating hormone (hFSH) of urinary source. Also, based on available data
19 derived from physio-chemical tests and bioassay, follitropin beta and follitropin alfa, another
20 recombinant follicle-stimulating hormone product, are indistinguishable.

21 Follistim[®] AQ Cartridge is a ready-for-use, pre-filled with solution, disposable cartridge
22 containing either 437.5 IU of follitropin beta in 0.525 mL (833 IU/mL) or 737.5 IU in 0.885 mL
23 (833 IU/mL) of aqueous solution for multiple dose use, with a maximal deliverable dose of either

24 **300 IU or 600 IU**, respectively. Other inactive ingredients in the cartridges include: sucrose 50
25 mg/mL, sodium citrate 14.7mg/mL, polysorbate 20 0.2 mg/mL, benzyl alcohol 10 mg/mL, L-
26 methionine 0.5 mg/mL and water for injection. Hydrochloric acid and/or sodium hydroxide are
27 used to adjust the pH to 7.

28 Follistim[®] AQ Cartridge is for use only with the Follistim Pen[™], which features an adjustable
29 dosing system for administering the drug in a microvolume of solution. The Follistim Pen[™]
30 with Follistim[®] AQ Cartridge is intended for SUBCUTANEOUS USE ONLY. The recombinant
31 protein in Follistim[®] AQ Cartridge has been standardized for FSH *in vivo* bioactivity in terms of
32 the First International Reference Preparation for human menopausal gonadotropins (code 70/45),
33 issued by the World Health Organization Expert Committee on Biological Standardization
34 (1982). Under current storage conditions, Follistim[®] AQ Cartridge may contain up to 11% of
35 oxidized follitropin beta.

36 In clinical trials with Follistim[®] (follitropin beta for injection), serum antibodies to FSH or anti-
37 CHO cell derived proteins were not detected in any of the treated patients after exposure to
38 Follistim[®] for up to three cycles.

39 Therapeutic Class: Infertility

40
41 ¹ As determined by the Ph. Eur. test for FSH *in vivo* bioactivity and on the basis of the molar extinction coefficient
42 at 277 nm ($\epsilon_s, \text{mg}^{-1} \text{cm}^{-1}$) = 1.066.

43

44 **CLINICAL PHARMACOLOGY**

45 Follicle stimulating hormone (FSH), the active component in Follistim[®] AQ (follitropin beta
46 injection) Cartridge, is required for normal follicular growth, maturation, and gonadal steroid
47 production. In women, the level of FSH is critical for the onset and duration of follicular

48 development, and consequently for the timing and number of follicles reaching maturity.
 49 Follistim[®] AQ Cartridge stimulates ovarian follicular growth in women who do not have primary
 50 ovarian failure. In order to effect the final phase of follicle maturation, resumption of meiosis
 51 and rupture of the follicle in the absence of an endogenous LH surge, human chorionic
 52 gonadotropin (hCG) must be given following treatment with Follistim[®] AQ Cartridge when
 53 patient monitoring indicates appropriate follicular development parameters have been reached.

54

55 **Pharmacokinetics**

56 The pharmacokinetics of Follistim[®] AQ Cartridge (follitropin beta injection) were evaluated in an
 57 open-labeled, single-center, randomized study in 20 healthy female subjects. A single
 58 subcutaneous injection of lyophilized Follistim[®] (follitropin beta for injection) which was
 59 reconstituted and administered by conventional syringe was compared to a single subcutaneous
 60 injection of Follistim[®] AQ Cartridge administered using the Follistim Pen[™]. The precision of the
 61 Follistim Pen[™] resulted in more efficient delivery of the ready-for-use solution contained in the
 62 Follistim[®] AQ Cartridge and an 18% increase in $AUC_{0-\infty}$ and C_{max} . The 18% difference found
 63 between serum FSH concentrations in subjects administered the two formulations was due to
 64 differences between the anticipated and actual volume delivered with the conventional syringe.
 65 The pharmacokinetic parameters for Follistim[®] AQ Cartridge are as follows:

66 TABLE 1: Mean (SD) Pharmacokinetic Parameters of a Single Subcutaneous Injection of 150
 67 IU of Follistim[®] AQ Cartridge (n=20)

68

	$AUC_{0-\infty}$ (IU/L·h)	C_{max} (IU/L)	t_{max} (h)	$t_{1/2}$ (h)	CL_{app} (L/h/kg)
Follistim [®] AQ Cartridge	215.1 (45.8)	3.4 (0.7)	12.9 (6.2)	33.4 (4.2)	0.01 (0.003)

69

70	AUC _{0-∞}	Area under the curve
71	C _{max}	Maximum concentration
72	t _{max}	Time to maximum concentration
73	t _{1/2}	Elimination half life
74	CL _{app}	Clearance

75

76 Absorption

77 The bioavailability of Follistim[®] following subcutaneous administration was investigated in
78 healthy, pituitary-suppressed, female subjects given a single 300 IU dose. After subcutaneous
79 injection the apparent dose absorbed was 77.8%.

80 In healthy, pituitary-suppressed, female subjects following a subcutaneous administration of 300
81 IU of Follistim[®], the AUC was 455.6±141.4 IU/L·h and C_{max} was 5.41±0.72 IU/L. A multiple,
82 dose proportionality, pharmacokinetic study of Follistim[®] was completed in healthy, pituitary-
83 suppressed, female subjects given subcutaneous doses of 75, 150, or 225 IU for seven days.
84 Steady-state blood concentrations of FSH were reached with all doses after five days of
85 treatment based on the minimum concentrations of FSH just prior to dosing (C_{min}). Peak blood
86 concentrations with the 75, 150, and 225 IU dose were 4.30±0.60, 8.51±1.16, and 13.92± 1.81
87 IU/L, respectively.

88 Distribution

89 The volume of distribution of Follistim[®] in healthy, pituitary-suppressed, female subjects
90 following intravenous administration of a 300 IU dose was approximately 8 L.

91 Metabolism

92 The recombinant FSH in Follistim[®] AQ Cartridge is biochemically similar to natural FSH, and it
93 is therefore, anticipated that it is metabolized in the same manner.

94 Elimination

95 The elimination half-life ($t_{1/2}$) following a single subcutaneous injection of 150 IU of
 96 Follistim[®] AQ Cartridge in female patients was 33.4 (4.2) hours. The clearance was 0.01 (0.003)
 97 L/h/kg.

98 Special Populations

99 The pharmacokinetics of Follistim[®] AQ Cartridge (follitropin beta injection) have not been
 100 determined in special populations such as geriatric, pediatric, renally impaired, and hepatically
 101 impaired patients.

102 Drug-Drug Interactions

103 Formal drug-drug interaction studies have not been conducted (see PRECAUTIONS).

104 **Clinical Studies**

105 The efficacy, tolerance, and ease of use of Follistim[®] AQ Cartridge (follitropin beta injection)
 106 administered using the Follistim Pen[™] were established in two US clinical studies [one study for
 107 Assisted Reproductive Technologies (ART) and one study for Ovulation Induction (OI)].

108 Assisted Reproductive Technologies (ART)

109 Results from an open-label, non-controlled, multi-center study in 60 women undergoing
 110 Controlled Ovarian Hyperstimulation (COH) for IVF or ICSI with Follistim[®] AQ Cartridge are
 111 summarized in Table 2.

112 **TABLE 2:** Results from an Open-label, Non-controlled, Multi-center Study in 60 Women
 113 Undergoing COH for IVF or ICSI with Follistim[®] AQ Cartridge Self-Administered With the
 114 Follistim Pen[™].

115

Parameter	Follistim [®] AQ Cartridge n=60
Mean(SD) number of oocytes recovered	13.9(10.3)

Mean(SD) total number of embryos obtained	7.2(5.5)
Median serum estradiol on the day of hCG (pg/mL)	1423.0 Range (469.5-4874.0)
Mean(SD) treatment duration (days)	9.0 (1.6)
Biochemical pregnancy rate/attempt (%)	56.7
Biochemical pregnancy rate/transfer (%)	61.8

116

117 Ovulation Induction (OI)

118 Results from an open-label, non-controlled, multi-center study in 43 clomiphene-resistant
119 women with chronic anovulation (WHO group II) who were treated with Follistim[®]AQ Cartridge
120 for induction of ovulation are summarized in Table 3.

121 **TABLE 3:** Results from an Open-label, Non-controlled, Multi-center Study in 43 Clomiphene-
122 resistant Women with Chronic Anovulation (WHO group II) Undergoing Ovulation Induction
123 with Follistim[®]AQ Cartridge Self-Administered with the Follistim Pen[™].

	Follistim[®]AQ Cartridge (n = 43)	n
Ovulation rate	95.3%	41
Biochemical pregnancy per attempt	34.9%	15

124

125 Ease of Use

126 In an observer questionnaire, designed to assess the "Ease of Use" of Follistim[®] AQ Cartridge
127 with the Follistim Pen[™], subjects rated their experience with the pen injector device. Subjects
128 undergoing ART and OI rated their injection experience in two separate studies. On Day 6 in the
129 ART group, more subjects rated the overall experience as "very good" as compared to Day 2, 54

130 subjects (90%) versus 49 subjects (81.8%), respectively and only one subject (1.7%) had a
131 "neutral" response. In the Ovulation Induction group, the experience rating of "very good"
132 increased from 90.7% on Day 2 to 95.2% on Day 8.

133

134 **INDICATIONS AND USAGE**

135 Follistim[®] AQ Cartridge (follitropin beta injection) is indicated for the development of multiple
136 follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART)
137 program. Follistim[®] AQ Cartridge is also indicated for the induction of ovulation and pregnancy
138 in anovulatory infertile patients in whom the cause of infertility is functional and not due to
139 primary ovarian failure.

140 **Selection of Patients**

141 Before treatment with Follistim[®] AQ Cartridge (follitropin beta injection) is initiated:

- 142 1) A thorough gynecologic and endocrinologic evaluation of the patient must be performed.
143 The evaluation should include a hysterosalpingogram (to rule out uterine and tubal
144 pathology) and documentation of anovulation by means of reviewing a patient's history,
145 performing a physical examination, determining serum hormonal levels as indicated, and
146 optionally performing an endometrial biopsy. Patients with tubal pathology should receive
147 Follistim[®] AQ Cartridge only if enrolled in an ART program.
- 148 2) Primary ovarian failure should be excluded by the determination of circulating gonadotropin
149 levels.
- 150 3) Careful examination should be made to rule out early pregnancy.
- 151 4) Evaluation of the partner's fertility potential should be included in the workup procedure.

152

153 **CONTRAINDICATIONS**

154 Follistim® AQ Cartridge (follitropin beta injection) is contraindicated in women who exhibit:

- 155 1) Prior hypersensitivity to recombinant hFSH products
- 156 2) A high circulating FSH level indicating primary ovarian failure
- 157 3) Uncontrolled thyroid or adrenal dysfunction
- 158 4) Tumor of the ovary, breast, uterus, hypothalamus, or pituitary gland
- 159 5) Pregnancy
- 160 6) Heavy or irregular vaginal bleeding of undetermined origin
- 161 7) Ovarian cysts or enlargement not due to polycystic ovary syndrome (PCOS)
- 162 8) Hypersensitivity reactions to streptomycin or neomycin. Follistim® AQ Cartridge may
- 163 contain traces of these antibiotics and may cause hypersensitivity reactions in susceptible
- 164 persons.

165

166 **WARNINGS**

167

168 **Follistim® AQ Cartridge (follitropin beta injection) should be used only by physicians who**

169 **are experienced in infertility treatment. Changes in brand (manufacturer), type**

170 **(recombinant, urinary, etc.), and/or method of administration (Follistim Pen™,**

171 **conventional syringe, etc.) may result in the need to adjust the dose. Follistim® AQ**

172 **Cartridge administered with the Follistim Pen™ contains a potent gonadotropic substance**

173 **and delivers on average an 18% higher amount of follitropin beta as compared to**

174 **lyophilized preparations administered by conventional syringe. Accordingly, a lower**

175 **starting dose for gonadotropin stimulation and dose adjustments during gonadotropin**

176 **stimulation should be considered for each woman treated with Follistim[®] AQ Cartridge (see**
177 **DOSAGE AND ADMINISTRATION).**

178

179 **Overstimulation of the Ovary During Treatment with Follistim[®] AQ (follitropin beta**
180 **injection) Cartridge.**

181 In order to minimize the hazards associated with the occasional abnormal ovarian enlargement
182 that may occur with Follistim[®] AQ Cartridge therapy, the lowest effective dose should be used
183 (see DOSAGE AND ADMINISTRATION). Use of ultrasound monitoring of ovarian response
184 and/or measurement of serum estradiol levels can further minimize the risk of overstimulation.

185 If the ovaries are abnormally enlarged on the last day of treatment with Follistim[®] AQ Cartridge,
186 hCG should not be administered in this course of treatment, to reduce the chances of developing
187 Ovarian Hyperstimulation Syndrome (OHSS).

188 Ovarian Hyperstimulation Syndrome (OHSS): OHSS is a medical entity distinct from
189 uncomplicated ovarian enlargement and may progress rapidly to become a serious medical event.

190 OHSS is characterized by a dramatic increase in vascular permeability, which can result in a
191 rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The
192 early warning signs of OHSS developing are severe pelvic pain, nausea, vomiting, and weight
193 gain. The following symptoms have been reported in cases of OHSS: abdominal pain,
194 abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe
195 ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal
196 hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural
197 effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see WARNINGS-
198 Pulmonary and Vascular Complications).

199 During clinical trials with Follistim[®] (follitropin beta for injection) and Follistim[®] AQ Cartridge
200 (follitropin beta injection) therapy, OHSS occurred in 60 (5.3%) of the 1132 women treated and
201 of these 33 (2.9%) were hospitalized. Cases of OHSS are more common, more severe, and more
202 protracted if pregnancy occurs; therefore, patients should be followed for at least two weeks after
203 hCG administration. Most often, OHSS occurs after treatment has been discontinued and it can
204 develop rapidly, reaching its maximum about seven to ten days following treatment. Usually,
205 OHSS resolves spontaneously with the onset of menses. If there is evidence that OHSS may be
206 developing prior to hCG administration (see PRECAUTIONS-Laboratory Tests), the hCG must
207 be withheld.

208 If serious OHSS occurs, treatment should be stopped and the patient should be hospitalized.
209 Treatment is primarily symptomatic and should consist of bed rest, fluid and electrolyte
210 management, and analgesics (if needed). Hemoconcentration associated with fluid loss into the
211 peritoneal cavity, pleural cavity, and the pericardial cavity may occur and should be thoroughly
212 assessed in the following manner: 1) fluid intake and output; 2) weight; 3) hematocrit; 4) serum
213 and urinary electrolytes; 5) urine specific gravity; 6) BUN and creatinine; 7) total proteins with
214 albumin: globulin ratio; 8) coagulation studies; 9) electrocardiogram to monitor for hyperkalemia
215 and 10) abdominal girth. These determinations should be performed daily or more often based
216 on clinical need.

217 OHSS increases the risk of injury to the ovary. The ascitic, pleural, and pericardial fluid should
218 not be removed unless there is the necessity to relieve symptoms such as pulmonary distress or
219 cardiac tamponade. Pelvic examination may cause rupture of an ovarian cyst, which may result
220 in hemoperitoneum, and should, therefore, be avoided. If bleeding occurs and requires surgical
221 intervention, the clinical objective should be to control the bleeding and retain as much ovarian

222 tissue as possible. Intercourse should be prohibited in patients with significant ovarian
223 enlargement after ovulation because of the danger of hemoperitoneum resulting from ruptured
224 ovarian cysts.

225 The management of OHSS may be divided into three phases: an acute, a chronic, and a
226 resolution phase. Because the use of diuretics can accentuate the diminished intravascular
227 volume, diuretics should be avoided except in the late phase of resolution as described below.

228 Acute Phase: Management during the acute phase should be directed at preventing
229 hemoconcentration due to loss of intravascular volume to the third space and minimizing the
230 risk of thromboembolic phenomena and kidney damage. Treatment is intended to normalize
231 electrolytes while maintaining an acceptable but somewhat reduced intravascular volume. Full
232 correction of the intravascular volume deficit may lead to an unacceptable increase in the amount
233 of third space fluid accumulation.

234 Management includes administration of limited intravenous fluids, electrolytes, human serum
235 albumin, and strict monitoring of fluid intake and output. Monitoring for the development of
236 hyperkalemia is recommended.

237 Chronic Phase: After stabilizing the patient during the acute phase, excessive fluid accumulation
238 in the third space should be limited by instituting severe potassium, sodium, and fluid restriction.

239 Resolution Phase: A fall in hematocrit and an increasing urinary output without an increased
240 intake are observed due to the return of the third space fluid to the intravascular compartment.

241 Peripheral and/or pulmonary edema may result if the kidneys are unable to excrete third space
242 fluid as rapidly as it is mobilized. Diuretics may be indicated during the resolution phase, if
243 necessary, to combat pulmonary edema.

244 **Pulmonary and Vascular Complications**

245 Serious pulmonary conditions (e.g., atelectasis, acute respiratory distress syndrome) have been
246 reported in women treated with gonadotropins. In addition, thromboembolic events both in
247 association with, and separate from, the Ovarian Hyperstimulation Syndrome have been reported
248 following gonadotropin therapy. Intravascular thrombosis, which may originate in venous or
249 arterial vessels, can result in reduced blood flow to vital organs or the extremities. Sequelae of
250 such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction,
251 cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. In rare
252 cases, pulmonary complications and/or thromboembolic events have resulted in death.

253

254 **Multiple Births**

255 Multiple births have been reported for all FSH treatments including Follistim[®] (follitropin beta
256 for injection) treatment. The patient and her partner should be advised of the potential risk of
257 multiple births before starting treatment.

258

259 **PRECAUTIONS**

260 **General**

261 Careful attention should be given to the diagnosis of infertility and in the selection of candidates
262 for treatment with Follistim[®] AQ Cartridge (follitropin beta injection) (see INDICATIONS AND
263 USAGE - Selection of Patients).

264

265 **Information for Patients**

266 Physicians must instruct patients on the correct usage and dosing of Follistim[®] AQ Cartridge in
267 conjunction with the Follistim Pen[™].

268 Patients should read and follow all instructions in the Follistim Pen™ Instructions for Use
269 manual/Treatment Diary prior to administration of Follistim® AQ Cartridge.

270 Prior to treatment with Follistim® AQ (follitropin beta injection) Cartridge patients should be
271 informed of the duration of treatment and monitoring procedures that will be required. The risks
272 of Ovarian Hyperstimulation Syndrome and multiple births (see WARNINGS), and other
273 possible adverse reactions (see ADVERSE REACTIONS) should be discussed.

274

275 **Laboratory Tests**

276 In most instances, treatment with Follistim® AQ Cartridge (follitropin beta injection) will result
277 only in follicular growth and maturation. In order to complete the final phase of follicular
278 maturation and to induce ovulation, hCG must be given following the administration of
279 Follistim® AQ Cartridge or when clinical assessment of the patient indicates that sufficient
280 follicular maturation has occurred. This may be directly estimated by sonographic visualization
281 of the ovaries and endometrial lining and/or measuring serum estradiol levels. The combination
282 of both ultrasonography and measurement of estradiol levels is useful for monitoring the growth
283 and development of follicles, timing hCG administration, as well as minimizing the risk of
284 OHSS and multiple gestations.

285 The clinical evaluation of estrogenic activity (changes in vaginal cytology, changes in
286 appearance and volume of cervical mucus, spinnbarkeit, and ferning of the cervical mucus)
287 provides an indirect estimate of the estrogenic effect upon the target organs, and therefore, it
288 should only be used adjunctively with more direct estimates of follicular development (e.g.,
289 ultrasonography and serum estradiol determinations).

290 The clinical confirmation of ovulation is obtained by direct and indirect indices of progesterone
291 production. The indices most generally used are as follows:

- 292 a) A rise in basal body temperature
- 293 b) Increase in serum progesterone
- 294 c) Menstruation following the shift in basal body temperature

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

- 298 a) Fluid in the cul-de-sac
- 299 b) Follicle showing marked decrease in size
- 300 c) Collapsed follicle

301

302 **Drug Interactions**

303 No drug/drug interaction studies have been performed.

304

305 **Carcinogenesis and Mutagenesis, Impairment of Fertility**

306 Long-term toxicity studies in animals have not been performed with Follistim[®] AQ Cartridge
307 (follitropin beta injection) to evaluate the carcinogenic potential of the drug. Follistim[®]
308 (follitropin beta for injection) was not mutagenic in the Ames test using *S. typhimurium* and *E.*
309 *coli* tester strains and did not produce chromosomal aberrations in an *in vitro* assay using human
310 lymphocytes.

311 **Pregnancy**

312 Pregnancy Category X (See CONTRAINDICATIONS).

313 **Nursing Mothers**

314 It is not known whether this drug is excreted in human milk. Because many drugs are excreted
 315 in human milk and because of the potential for serious adverse reactions in the nursing infant
 316 from Follistim® AQ Cartridge (follitropin beta injection), a decision should be made whether to
 317 discontinue nursing or to discontinue the drug taking into account the importance of the drug to
 318 the mother.

319 **Pediatric Use**

320 Safety and effectiveness in pediatric patients have not been established.

321 **Geriatric Use**

322 Clinical studies did not include subjects aged 65 and over.

323

324 **ADVERSE REACTIONS**

325 **Assisted Reproductive Technologies (ART)**

326 Rates of adverse events from an open-label, non-controlled, multi-center study in 60 women
 327 undergoing COH for IVF or ICSI with Follistim® AQ Cartridge administered with the Follistim
 328 Pen™ are summarized in Table 4

329 **TABLE 4:** Incidence of Adverse Clinical Experiences (≥5%)

330

Adverse Event	Follistim® AQ Cartridge n=60
Abdominal pain	28 %
Flatulence	27 %
Abdominal pain, gynecological	25 %

Nausea	17%
Breast pain, female	15 %
Injection site reaction	10 %
Abdomen enlarged	8 %
Back pain	7 %
Constipation	5 %
Headache	5 %
Ovarian pain	5 %

331

332 **Ovulation Induction**

333 Rates of adverse events from an open-label, non-controlled, multi-center study in 43 clomiphene-
 334 resistant women with chronic anovulation (WHO group II) undergoing Ovulation Induction with
 335 Follistim[®]AQ Cartridge administered with the Follistim Pen[™] are summarized in Table 5.

336

337 **TABLE 5:** Incidence of Adverse Clinical Experiences (≥5%)

Adverse Event	Follistim [®] AQ Cartridge n=43
Ovarian hyperstimulation syndrome	9 %
Abdominal pain	5 %
Injection site reaction	5 %
Sinusitis	5 %
Upper respiratory tract infection	5 %

338

339 The following adverse events have been reported in women treated with gonadotropins:
340 pulmonary and vascular complications (see WARNINGS), hemoperitoneum, adnexal torsion (as
341 a complication of ovarian enlargement), dizziness, tachycardia, dyspnea, tachypnea, febrile
342 reactions, flu-like symptoms including fever, chills, musculoskeletal aches, joint pains, nausea,
343 headache and malaise, breast tenderness, and dermatological symptoms (dry skin, erythema,
344 body rash, hair loss and hives).

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

348 **Congenital Anomalies**

349 The incidence of congenital malformations after Assisted Reproductive Technologies (ART)
350 may be slightly higher than after spontaneous conception. This slightly higher incidence is
351 thought to be related to differences in parental characteristics (e.g., maternal age, sperm
352 characteristics) and to the higher incidence of multiple gestations after ART. There are no
353 indications that the use of gonadotropins, during ART is associated with an increased risk of
354 congenital malformations.

355 **DRUG ABUSE AND DEPENDENCE**

356 There have been no reports of abuse or dependence with Follistim[®]AQ (follitropin beta
357 injection) Cartridge.

358

359 **OVERDOSAGE**

360 Aside from the possibility of Ovarian Hyperstimulation Syndrome [see WARNINGS-
361 Overstimulation of the Ovary During treatment with Follistim[®]AQ Cartridge (follitropin beta

362 injection) and multiple gestations (see WARNINGS-Multiple Births)], there is no additional
 363 information concerning the consequences of acute overdosage with Follistim® AQ Cartridge.

364 **DOSAGE AND ADMINISTRATION**

365 When administering Follistim® AQ Cartridge, a lower starting dose for gonadotropin stimulation
 366 and dose adjustments during gonadotropin stimulation should be considered for each patient.

367 For that purpose the following Dose Conversion Table might be a useful reference.

368
 369 **TABLE 6:** Follistim® AQ Cartridge (follitropin beta injection) Administered with the Follistim
 370 Pen™ Dose Conversion Table*
 371

Lyophilized recombinant FSH dosing in ampules or vials using conventional syringe	Follistim® AQ Cartridge dosing with the Follistim Pen™
75 IU	50 IU
150 IU	125 IU
225 IU	175 IU
300 IU	250 IU
375 IU	300 IU
450 IU	375 IU

372
 373 *Each value represents an 18% difference rounded to the nearest 25 IU increment.

374
 375 Follistim® AQ Cartridge (follitropin beta injection) is delivered by the Follistim Pen™ which
 376 accurately delivers the dose to which it is set. In a clinical bioavailability study that compared
 377 administration of the dissolved lyophilized follitropin beta preparation using a conventional
 378 syringe and needle and a ready-to-use follitropin beta solution in a cartridge injected with the pen
 379 device, it was shown that the pen device delivered, on average of an 18% higher amount of
 380 follitropin beta.

381 This difference is due to the accurate dosing obtained with the Follistim Pen™ compared to a
 382 conventional syringe. This 18% difference corresponds to a similar difference in serum FSH

383 concentrations caused by differences between the anticipated and the actual volume of follitropin
384 beta injected with the conventional syringe.

385 **Assisted Reproductive Technologies (ART)**

386 In an open-label, non-controlled, multi-center study, 60 women who were undergoing COH for
387 IVF with and without ICSI were treated with Follistim[®] AQ Cartridge at a starting dose of 150 to
388 225 IU for the first 5 days of treatment. This dose could be adjusted after that time based upon
389 ovarian response. The maximum, individualized, daily dose of Follistim[®] AQ Cartridge used in
390 this clinical study was 450 IU.

391 A starting dose of 150 to 225 IU or lower of Follistim[®] AQ Cartridge (follitropin beta injection)
392 is recommended for at least the first 5 days of treatment. If a prescriber generally uses a starting
393 dose of 150 to 225 IU of lyophilized gonadotropin, then the prescriber should consider using a
394 lower starting dose of Follistim[®] AQ Cartridge. (See Dose Conversion Table). After this, the
395 dose may be adjusted for the individual patient based upon her ovarian response. For Follistim[®]
396 AQ Cartridge, lower maintenance doses should be considered for each patient.

397 During treatment with Follistim[®] AQ Cartridge, when a sufficient number of follicles of adequate
398 size are present, the final maturation of the follicles is induced by administering hCG at a dose of
399 5000 to 10,000 IU. Oocyte (egg) retrieval is performed 34 to 36 hours later. The administration
400 of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of
401 treatment with Follistim[®] AQ Cartridge. This will reduce the chance of developing OHSS.

402 **Ovulation Induction**

403 In an open-label, non-controlled, multi-center study in 43 clomiphene-resistant women with
404 chronic anovulation (WHO group II) who were treated with Follistim[®] AQ Cartridge for
405 induction of ovulation, a stepwise increasing dose regimen was included. The starting dose was

406 75 IU of Follistim[®] AQ Cartridge (follitropin beta injection) for up to 7 days. The dose was
407 increased by either 25 IU or 50 IU at weekly intervals until follicular growth and/or serum
408 estradiol levels indicated an adequate ovarian response. The maximum, individualized daily dose
409 of Follistim[®] AQ Cartridge that had been used for ovulation induction patients during this clinical
410 trial is 175 IU.

411 A starting dose of 75 IU or lower of Follistim[®] AQ Cartridge (follitropin beta injection) is
412 recommended for at least the first 7 days of treatment with dose adjustments at weekly intervals
413 based upon patient response. If a prescriber generally uses a starting dose of 75 IU of lyophilized
414 gonadotropin, then the prescriber should consider using a lower starting dose of Follistim[®] AQ
415 Cartridge (See Dose Conversion Table).

416 Treatment should continue until ultrasonic visualizations and/or serum estradiol determinations
417 indicate pre-ovulatory conditions equivalent to or greater than those of the normal individual
418 followed by hCG, 5000 to 10,000 IU. If the ovaries are abnormally enlarged on the last day of
419 treatment with Follistim[®] therapy, hCG must be withheld during this course of treatment; this
420 will reduce the chances of developing OHSS.

421 During treatment with Follistim[®] AQ Cartridge (follitropin beta injection) and during a two week
422 post-treatment period, patients should be examined at least every other day for signs of excessive
423 ovarian stimulation. It is recommended that treatment with Follistim[®] AQ Cartridge be stopped
424 if the ovaries become abnormally enlarged or abdominal pain occurs. Most OHSS occurs after
425 treatment has been discontinued and reaches its maximum at about seven to ten days post-
426 ovulation.

427 For ovulation induction, the couple should be encouraged to have intercourse daily, beginning on
428 the day prior to the administration of hCG and until ovulation becomes apparent from the indices

429 employed for the determination of progestational activity (see PRECAUTIONS-Laboratory
430 Tests). Care should be taken to insure insemination. In the light of the foregoing indices and
431 parameters mentioned, it should become obvious that, unless a physician is willing to devote
432 considerable time to these patients and be familiar with and conduct these necessary laboratory
433 studies, he/she should not use Follistim[®] AQ Cartridge.

434 Parenteral drug products should be inspected visually for particulate matter and clarity prior to
435 administration whenever solution and container permit. Do not use solution if particulate matter
436 is present.

437 No other drugs should be added or combined into the Follistim[®] AQ Cartridge.

438

439 **HOW SUPPLIED**

440 Follistim[®] AQ Cartridge (follitropin beta injection) is supplied in a box containing 4 disposable,
441 29 gauge, ultra-fine, ½ inch, sterile BD Micro-Fine™ Pen Needles (for use with Follistim Pen™
442 available separately) and one disposable, blister packed, prefilled 1.5 mL colorless glass
443 cartridge, with grey rubber piston and an aluminium crimp-cap with black rubber inlay and in the
444 following presentations:

445

446 NDC 0052-0313-01 Follistim[®] AQ Cartridge 437.5 IU/0.525 mL (delivering 300 IU)

447 with silver crimp- caps

448 NDC 0052-0316-01 Follistim[®] AQ Cartridge 737.5 IU /0.885 mL (delivering 600 IU)

449 with gold crimp-caps

450

451 **Storage**

452 Store refrigerated, 2-8° C (36-46° F) until dispensed. Upon dispensing, the product may be
453 stored by the patient at 2-8° C (36-46° F) until the expiration date, or at 25°C (77°F) for 3
454 months or until expiration date, whichever occurs first. Once the rubber stopper of the
455 Follistim® AQ Cartridge has been pierced by a needle, the product can only be stored for a
456 maximum of 28 days at 2-25 °C (36-77 °F). Protect from light. Do not freeze.

457 For more information, call
458 1-866-836-5633
459 Rx only



460

461 Manufactured for Organon USA Inc.
462 West Orange, NJ 07052
463 by Vetter Pharma-Fertigung GmbH & Co. KG
464 Ravensburg, Germany
465 and packaged by Organon (Ireland) Ltd, Swords
466 County Dublin, Ireland
467

468 5310202

0304

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43

Patient Information Leaflet

Follistim[®] AQ Cartridge
(follitropin beta injection)

300 IU and 600 IU

Read the patient information carefully before you start using Follistim[®] AQ (fol-i-stim) Cartridge with Follistim Pen™ and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is Follistim[®] AQ Cartridge?

Follistim[®] AQ Cartridge (follitropin beta injection) is a medicine that contains the hormone follicle stimulating hormone (FSH). FSH may help (stimulate) the ovaries to make eggs in women who have fertility problems. FSH will not help women who have a condition called primary ovarian failure.

What is Follistim[®] AQ Cartridge used for?

Follistim[®] AQ Cartridge (follitropin beta injection) is used:

- a. To help women who have problems with ovulation. Follistim[®] AQ Cartridge will not help women whose ovaries do not work at all (primary ovarian failure).
- b. For women that are in an Assisted Reproductive Technology (ART) program, such as *in vitro* fertilization.

If you have previously used gonadotropins, your dose may be different with Follistim[®] AQ Cartridge.

Always follow your doctor's dosing instructions when administering Follistim[®] AQ Cartridge. Your doctor has individualized the dose to be administered based on your medical history. Do not change your dose unless instructed by your doctor.

Who should not take Follistim[®] AQ Cartridge?

Do not use Follistim[®] AQ Cartridge if you:

- are allergic to recombinant human FSH products (see the end of this leaflet for a list of all the ingredients in Follistim[®] AQ Cartridge)
- have primary ovarian failure (your ovaries do not work at all)
- are pregnant, or think you might be pregnant
- have uncontrolled thyroid or adrenal gland problems
- have tumors in your ovaries, breasts, uterus, hypothalamus, or pituitary gland
- have heavy or irregular vaginal bleeding and the cause is not known
- have ovarian cysts or enlarged ovaries, not due to polycystic ovary syndrome (PCOS)
- are allergic to streptomycin or neomycin. Follistim[®] AQ Cartridge may contain traces of these antibiotics and may cause allergic reactions

44 **Tell your healthcare provider if you are breast feeding.** It is not known if Follistim® AQ passes
45 into your milk.

46
47 **What are the possible side effects of Follistim® AQ Cartridge?**

48 Follistim® AQ Cartridge may cause serious side effects. This can happen if too much Follistim® AQ
49 Cartridge is used or it is not used the right way.

- 50
51 • **Ovarian Hyperstimulation Syndrome (OHSS).** OHSS is a serious medical problem that
52 can happen when the ovaries are overstimulated. In rare cases it has caused death. OHSS
53 causes fluid to build up suddenly in the stomach and chest areas. OHSS may occur after
54 treatment with Follistim® AQ Cartridge.

55
56 Call your healthcare provider right away if you get any of the following symptoms:

- 57 - severe pelvic pain (lower stomach area)
58 - nausea
59 - vomiting
60 - sudden weight gain
61 - reduced urine output
- 62
63 • **Lung and blood vessel problems.** Follistim® AQ Cartridge and other FSH products may
64 cause serious lung problems including fluid in the lungs (atelectasis) and acute respiratory
65 distress syndrome (ARDS). Follistim® AQ Cartridge and other FSH products may also cause
66 blood clots in blood vessels. This can lead to blood vessel problems (thrombophlebitis),
67 stroke, loss of limb, or a blood clot in the lung (pulmonary embolus).
- 68
69 • **Multiple births.** Follistim® AQ Cartridge and other FSH products can cause multiple births.
70 Your healthcare provider will discuss your chances of multiple births.
- 71
72 • Other side effects with Follistim® AQ Cartridge include stomach pain, gas, pelvic pain,
73 nausea, breast pain, injection site problems, enlarged stomach area, back pain, constipation,
74 headache and ovarian pain. If you get any side effects that concern you, call your healthcare
75 provider.

76
77 These are not all the side effects of Follistim® AQ Cartridge. Contact your doctor without delay if
78 you are experiencing symptoms including significant abdominal pain, or if symptoms develop some
79 days after the last injection has been given (see also, “Who should not take Follistim® AQ
80 Cartridge?”, section of this leaflet).

81
82
83 **How should I use Follistim® AQ Cartridge?**

- 84 • Your healthcare provider will decide on the dose of Follistim® AQ Cartridge (follitropin
85 beta injection) that is best for you. This dose may be increased or decreased as your
86 treatment goes on. This will depend on your type of treatment. It is very important that you
87 follow your healthcare provider’s instructions exactly.
- 88
89 • Follistim® AQ Cartridge is given by an injection just under the skin (subcutaneous injection).

90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133

Your healthcare provider’s office will teach you how to inject yourself. See the end of this leaflet for “Instructions For Use”. Do not inject Follistim®AQ Cartridge at home until your healthcare provider’s office has taught you the right way.

Close care by your healthcare provider is very important. Usually ultrasound scans (special x-rays) of the ovaries are regularly made. Blood or urine samples are regularly taken. The results of these tests allow your healthcare provider to choose the right dose of Follistim®AQ Cartridge for you each day. This is very important. Too high a dose of FSH may lead to rare, but serious problems in which the ovaries become overstimulated (too active). This may be noticed as pain in the abdomen (stomach area). Regular checking of your response to FSH treatment helps your healthcare provider lower your chances of ovarian overstimulation. Call your healthcare provider right away if you get strong abdominal pain. Also call your healthcare provider right away if this happens some days after the last injection has been given.

Dosage

- **Assisted Reproductive Technologies (ART)**

A starting dose of Follistim®AQ Cartridge (follitropin beta injection) will be prescribed by your doctor based upon review of your medical history. This starting dose of Follistim®AQ Cartridge to be injected with the Follistim Pen™ under the skin is usually recommended for at least the first 5 days of treatment. After this, your doctor may adjust your dose based upon how your ovaries are responding to Follistim®AQ Cartridge. When an ultrasound examination shows that you are ready, another drug (hCG) may be injected to induce the final maturation of the follicles.

- **Ovulation Induction**

A starting dose of Follistim®AQ Cartridge (follitropin beta injection) will be prescribed by your doctor based upon review of your medical history. This starting dose of Follistim®AQ Cartridge to be injected with the Follistim Pen™ under the skin is usually recommended for at least 7 days. Your doctor may then adjust the dose based upon how your ovaries are responding to Follistim®AQ Cartridge. When an ultrasound examination shows that you are ready, another drug (hCG) may be injected to induce ovulation.

WHAT YOU WILL NEED FOR GIVING YOURSELF THE INJECTION

- Follistim Pen™, a Follistim®AQ Cartridge, the BD Micro-Fine™ Pen Needle provided with the cartridge.
- Alcohol, cotton balls or alcohol pads/swabs, sterile gauze, antibacterial soap and a special safety container to discard the used needles, cartridges and/or other supplies.

134

IMPORTANT NOTICE

135

Please read all instructions for the use of the Follistim Pen™ before administering the Follistim® AQ Cartridge.

136

137

1. The Follistim Pen™ is a precision medical device. It is very important that you read and follow all directions for its use. As with all injection systems, failure to do so could result in an incorrect dose being given.

138

139

140

2. Injecting cold drug is likely to cause discomfort. Therefore, it is recommended you allow the drug to reach room temperature before taking the injection. The needle should not be attached until just before the injection.

141

142

143

3. When injecting beneath the skin, always fully depress the Injection Button for a full 5 seconds. During these 5 seconds, leave the needle in the skin to ensure delivery of the full dose of Follistim® AQ Cartridge.

144

145

146

4. Follistim Pen™ is designed for use by one person only and should not be shared with others.

147

148

5. The BD Micro-Fine™ Pen Needle is for use only with Follistim Pen™. Each BD Micro-Fine™ Pen Needle is for one injection only.

149

150

6. Follistim Pen™ is not recommended for the blind or visually impaired user without the assistance of an individual with good vision, trained in the proper use of the device.

151

152

7. It is advisable to keep a record of every injection that has been taken from a Follistim® AQ Cartridge. A patient diary is available with the Instructions for Use Manual. This will allow you to calculate the daily amount of medication remaining in the cartridge by subtracting the injected amount from the 300 IU and/or 600 IU as indicated on the cartridge label.

153

154

155

8. Your doctor will decide on the dose of Follistim® AQ Cartridge to be given. This dose may be increased or decreased as your treatment progresses depending on your individual type of treatment. If you have previously used gonadotropins, your dose may be different with Follistim® AQ Cartridge. Again, your doctor will decide the dose based upon your medical history.

156

157

158

159

160 **INSTRUCTIONS FOR USE**

161 **BEFORE USING FOLLISTIM PEN™ FOR THE FIRST TIME, READ THESE**
162 **INSTRUCTIONS CAREFULLY. THEY ARE DIVIDED INTO SECTIONS. EACH**
163 **SECTION HAS A NUMBER OF STEPS.**

164 **KEEP THIS LEAFLET IN A SAFE PLACE AND REFER TO IT WHEN QUESTIONS**
165 **ARISE.**

166 The main actions contained in this patient leaflet that must be learned are:

167 **1. Loading the Follistim Pen™**

168
169 **2. Dialing the prescribed dose**

170
171 **3. Using the Follistim Pen™ to give yourself an injection of Follistim® AQ Cartridge**

172
173 The Follistim Pen™ is a very precise injection device. It is easy to use and convenient. The special
174 features allow you to inject Follistim® AQ Cartridge safely and effectively.

175
176 Follistim Pen™ can be set to any dose from 50 International Units (IU) up to 450 IU, in marked
177 increments. The Dosage Scale on the Pen has easy-to-read numbers and audible clicks to help you
178 set the correct dose. Incorrect settings are easily corrected without loss of drug.

179
180 • Follistim® AQ Cartridges and BD Micro-Fine™ Pen Needles may only be used with Follistim
181 Pen™.

182 • Do not separate the three parts of the Follistim Pen™ shown below, until told to do so in the
183 instructions.

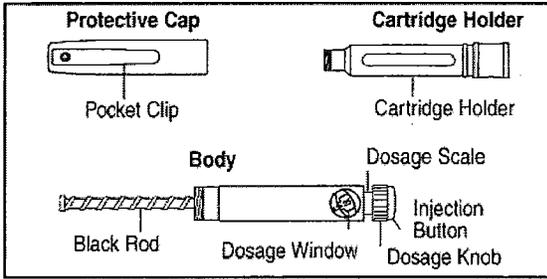
184
185 **INJECTION INSTRUCTIONS FOR FOLLISTIM® AQ CARTRIDGE WITH THE**
186 **FOLLISTIM PEN™**

187 **Carefully read these instructions before injecting Follistim® AQ Cartridge with the Follistim**
188 **Pen™. Do not use Follistim® AQ Cartridge with the Follistim Pen™ unless your healthcare**
189 **provider has taught you the right way to inject it and you understand everything. Ask your**
190 **healthcare provider if you have any questions.**

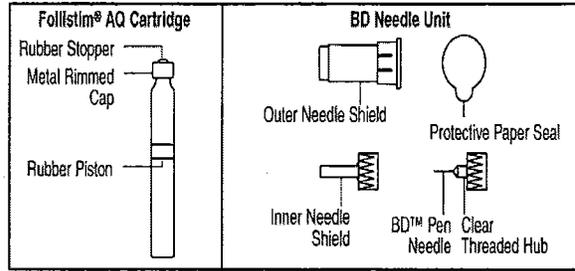


Figure shown not actual size

Follistim Pen™ Parts



Follistim® AQ Cartridge and BD Needle Unit Parts



202

203

204

USING THE FOLLISTIM PEN™

205 **Follow these steps:**

206

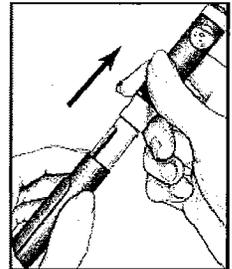
- 207 • Before you use the Follistim Pen™ for the first time
- 208 • When you replace the cartridge

209 Note: Always wash your hands thoroughly with antibacterial soap and water before you use the
210 Follistim Pen™ or when you replace the cartridge.

211

212

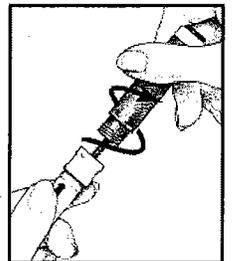
- 213 1. While holding the Pen Body firmly with one hand, pull off the Protective Cap
214 with your other hand. Put the cap aside on a clean, dry surface.



215

216

- 217 2. Unscrew the entire Pen Body from the Cartridge Holder. Place the Cartridge
218 Holder and the Pen Body aside on a clean, dry surface.

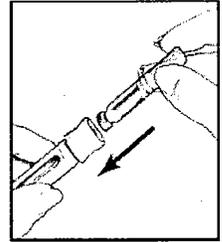


219

LOADING THE FOLLISTIM PEN™

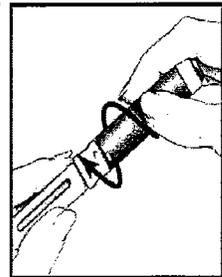
220

221 3. Take a Follistim® AQ Cartridge out of its package. Do not use the
222 Follistim®AQ Cartridge if the medicine contains particles or it is not clear.
223 Make sure the medicine is at room temperature before using. Clean the Rubber
224 Stopper on the cartridge with an alcohol pad. Pick up the Cartridge Holder and
225 place the cartridge into the Cartridge Holder. Insert the Metal Rimmed Cap end
226 first.



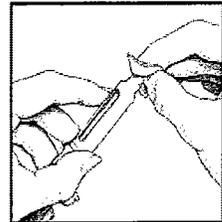
227

228 4. Pick up the Pen Body and lower it into the Cartridge Holder. The black
229 rod must press against the Rubber Piston on the cartridge. Screw the Pen
230 Body fully onto the Cartridge Holder. Make sure there is no gap between
231 the Pen Body and the Cartridge Holder. The arrow (▲) on the Cartridge
232 Holder should point to the middle of the yellow alignment mark (■) on
233 the blue Pen Body.



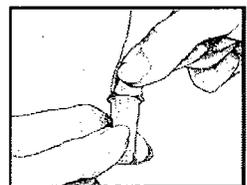
234

235 5. You must use a new BD Micro-Fine™ Pen Needle with each injection. Never
236 reuse a needle. Attach a BD Micro-Fine™ Pen Needle after you make sure
237 there is a Follistim® AQ Cartridge in the Cartridge Holder. Clean the open end
238 of the Cartridge Holder with an alcohol pad.



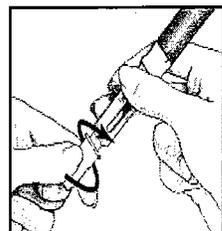
239

240 6. Pick up your BD Micro-Fine™ Pen Needle that is in an Outer Needle Shield.
241 Peel off the protective paper seal. Do not touch the needle or place an open
242 needle on any surface.



243

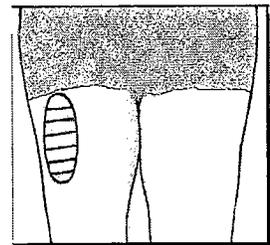
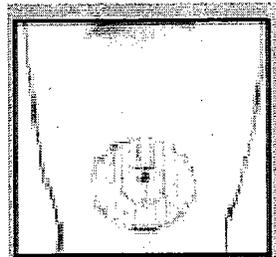
244 7. Hold the Outer Needle Shield firmly in one hand while holding the Cartridge
245 Holder firmly in the other hand. Push the end of the Cartridge Holder into the



246 Outer Needle Shield. Screw them tightly together. Place your Follistim Pen™ with the attached
247 needle, flat on a clean, dry surface.

248

249 8. The best place for injection is in the abdomen, which is the stomach area below the belly button
250 (navel) or in the upper leg. Your healthcare provider can show you other places where you can
251 inject Follistim® AQ Cartridge. Change your injection site a little bit with each injection to lower
252 your chances for skin reactions.



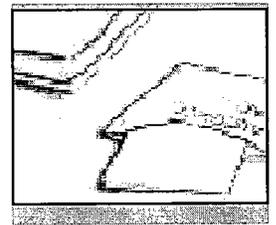
253

254

255

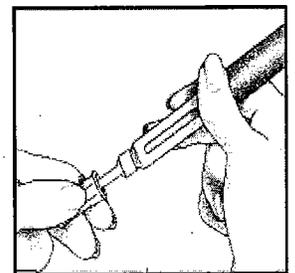
256

257 9. Use a swab moistened with alcohol to clean the skin area where the needle will
258 enter to remove any surface bacteria. Clean about two inches around the
259 injection site where the needle will be inserted. Let the alcohol dry on your
260 skin for at least one minute before injecting the medicine.



261

262 10. Pull the Outer Needle Shield gently, leaving the Inner Needle Shield in place
263 (covering the needle, which is now attached to the Pen). ***Do not throw the***
264 ***Outer Needle Shield away.*** You will need it to dispose of the needle after
265 injecting the medicine. Instructions for disposing the needle are given later in
266 this leaflet.



267

268 **Important:**

- 269 • **Do not touch the needle or leave it uncapped without Inner Needle Shield so that it**
270 **remains sterile.**
- 271 • **Use a new, sterile BD Micro-Fine™ Pen Needle for each injection. Only use the BD Micro-**
272 **Fine™ 0.33 mm x 12.7 mm (29G) Pen needles as supplied with the Follistim® AQ**
273 **Cartridge.**

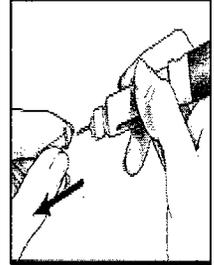
274

275

276

277

278 11. Carefully remove the Inner Needle Shield and discard it. *Do not touch the*
279 *needle or let it touch any surface while uncapped.*



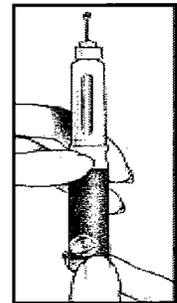
280

281

282

283

284 12. Hold the Follistim Pen™ with the needle pointing upwards. Tap the Cartridge
285 Holder gently with your finger to help air bubbles rise to the top of the needle.
286 The small amount of air bubble will not affect the amount of medicine you
287 receive. Look for a droplet forming at the tip of the needle. If you see a droplet,
288 go to Step 13.



289 If you do not see a droplet, continue with this step.

290 If you do not see a droplet at the tip of the needle:

- 291 a. Dial the Dosage Knob until you hear one click. With the needle pointing upwards,
292 push in the Injection Button.
- 293 b. Look for the droplet.
- 294 c. If you still do not see a droplet, repeat Step a. (above) until you see droplet. You
295 must make sure you see a droplet of medicine or you may not inject the right amount
296 of medicine.

297

298 **Important:**

- 299 • **Always check the drug flow by following the directions in Step 12. This will ensure that**
300 **the correct dose of Follistim® AQ Cartridge is injected. If you do not check drug flow, you**
301 **may receive less drug than the dose that you dialed.**

302

303

304

DIALING THE PRESCRIBED DOSE

305

13. Your Follistim[®]AQ Cartridge will contain either 300IU or 600IU. Record the Follistim[®]AQ Cartridge content in your Follistim Pen[™] Treatment Diary (refer to CHECKING THE DRUG LEVEL for more information). For doses of 50 IU up to 450 IU, turn the Dosage Knob until the dot beside the correct number on the Dosage Scale is sitting in the middle of the Dosage Window.

306

307

308

309

310

311

312

14. If by mistake you dial past the correct number, *do not try to turn the Dosage Knob backward to fix the mistake.* Continue to turn the Dosage Knob in the same direction past the 450 IU mark, as far as it will turn. The Dosage Scale must move freely. Push the Injection Button in all the way. Start to dial again starting from "0" upwards.

313

314

315

316

317

By following these directions, you will not lose any medicine from the Follistim[®]AQ Cartridge.

318

319

320

Important:

322

•If you do turn the Dosage Knob backward to correct the mistake, it will not hurt the Pen, but you will lose some drops of Follistim[®] AQ Cartridge from the tip of the needle.

323

324

•Never dial your dose or try to correct a dialing mistake when the needle is still in your skin as this may result in your receiving an incorrect dose.

325

326

327

328

USING THE FOLLISTIM PEN[™] TO GIVE YOURSELF AN INJECTION OF FOLLISTIM[®]AQ CARTRIDGE

329

330

Once you have set the Follistim Pen[™] to the correct dose, you are ready for your injection.

332

333

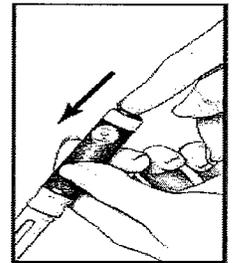
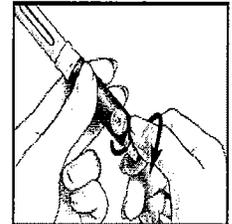
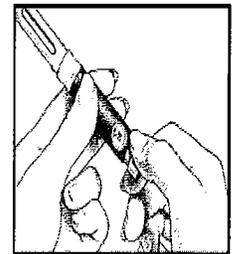
334

15. Pinch the already swabbed area of the skin between two fingers. With the other hand, insert the entire BD Micro-Fine[™] Pen Needle straight into the skin. Press the injection button all the way in to make sure you give yourself a full injection. Wait for five seconds before pulling the needle out of the skin. The

335

336

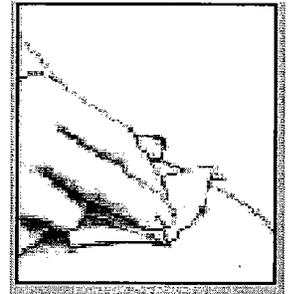
337



338 middle of the Dosage Window should display a dot next to the “0”. If the injection button does
339 not push in all the way, and the number in the Dosage Window does not read “0”, it means there
340 is not enough medication left in the cartridge. The number in the Dosage Window will give you
341 the amount of medicine needed to complete your dose. Write this number down. This will be
342 the number you dial for the completion of your dose. Start over with a new Follistim®AQ
343 Cartridge and a new needle and follow all the instructions up to this step. Make sure you choose
344 a different injection site to complete your dose of Follistim®AQ Cartridge.

345
346
347
348
349
350
351
352

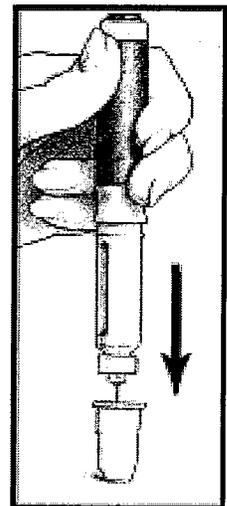
16. Pull out the BD Micro-Fine™ Needle and firmly press down on the injection site with an alcohol swab. Use the BD Micro-Fine™ Pen Needle for one injection only.



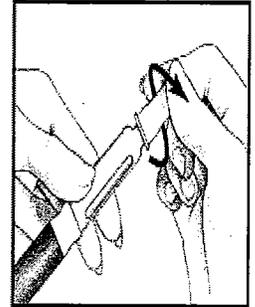
353 **Important:**

- 354 • **If the dot next to the “0” is not in the middle of the Dosage Window and you cannot**
355 **push the Injection Button all the way in, do not try to force down the button. Your**
356 **Follistim®AQ Cartridge is probably empty. This means you have not received your**
357 **full dose. Do not adjust the setting on the Dosage Scale. Follow the instructions for IF**
358 **THERE IS NOT ENOUGH FOLLISTIM®AQ IN THE CARTRIDGE.**

359 17. Place the Outer Needle Shield on a flat table surface with the opening pointing up. The opening
360 of the Outer Needle Shield is the wider end with the rim. Without holding on to
361 the Outer Needle Shield, carefully insert the needle (attached to the Follistim
362 Pen™) into the opening of the Outer Needle Shield and push down firmly. The
363 Outer Needle Shield should now be attached to the Cartridge Holder and cover
364 the needle.



365 18. Grip the Outer Needle Shield and use it to unscrew the needle from the
366 Cartridge Holder. Your healthcare provider can advise you on how to obtain a
367 special container for proper needle disposal. Safely, dispose the Outer Needle
368 Shield with the used needle right away. Do not throw away in a trash can. If
369 there is Follistim[®] AQ Cartridge medicine left for more injections, put the Pen
370 Cap back on the Pen Body and store your Follistim Pen[™] in a safe place in the
371 refrigerator (**not in the freezer**) or at room temperature. *Never store the*
372 *Follistim Pen[™] with a needle attached to it.*

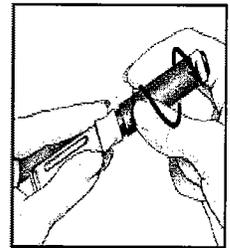


373 **Important:**

- 374 • **Use the BD Micro-Fine[™] Pen Needle for one injection only. Dispose of the used needle**
375 **inside the Outer Needle Shield immediately in a properly secured container as instructed**
376 **by your healthcare professional.**
- 377 • **Always unscrew the needle by following the directions in Steps 17 and 18 before you put**
378 **the Follistim Pen[™] away.**
- 379 • **Never store the Follistim Pen[™] with a needle attached to it. If you store the Follistim**
380 **Pen[™] with the needle attached, the drug could leak out and there is risk of contamination.**
- 381 • **Never leave needles where others can pick them up.**

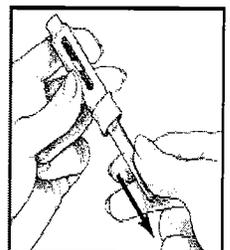
382

383 19. Before you remove the empty Follistim[®] AQ Cartridge from the Follistim
384 Pen[™], unscrew the needle by following Steps 17 and 18. Unscrew the Pen
385 Body from the Cartridge Holder.



386

387 20. Put the Pen Body down on a clean, dry surface and remove the empty
388 Follistim[®] AQ Cartridge from the Cartridge Holder. Safely, dispose of the
389 empty Follistim[®] AQ Cartridge right away in the same special container that
390 you used for the needle disposal. Do not put the cartridge in a trash can.



391

392

393 **Now, you may either:**

394 • Put the Follistim Pen™ back together without a Follistim® AQ Cartridge and store for your next
395 injection

396 **OR**

397 • Insert a new Follistim® AQ Cartridge into the Cartridge Holder, put your Follistim Pen™ back
398 together, and store safely in the refrigerator or at room temperature.

399

400

401

CHECKING THE DRUG LEVEL

402 When you are advised on the number of prescribed doses which can be extracted from the full
403 unused Follistim® AQ Cartridge (follitropin beta injection), then do not use the cartridge beyond the
404 advised number of doses. Otherwise, you will run the risk that there will not be enough volume of
405 drug for your prescribed dose.

406 Starting with the initial injection, you should begin using your Follistim Pen™ Treatment Diary as
407 follows:

408 a. Record the Follistim® AQ Cartridge content. This will either be 300 or 600 IU depending on
409 what your doctor has prescribed for you.

410 b. Record the daily dose you have been prescribed for your injection.

411 c. Subtract your Day 1 dose from the Follistim® AQ Cartridge content (300 or 600 IU) (see
412 example below). This will give you the remaining Follistim® AQ Cartridge content.

413

414 After Day 1, continue to record your daily injections in your Treatment Diary as follows:

415 d. Place the number recorded on Day 1 in the remaining Follistim® AQ Cartridge contents box in
416 the Day 2 Follistim® AQ Cartridge content box.

417 e. Subtract your Day 2 dose from the Follistim® AQ Cartridge content you just recorded in Step d.
418 This will give you the remaining Follistim® AQ Cartridge content. Again, record this number in
419 the correct box.

420

421

422

423

Date	Daily Dose to be Used (IUs/day)	Follistim [®] AQ Cartridge Content	Remaining Follistim [®] AQ Cartridge Content
mm/dd /yy	150	600	450
mm/dd/yy	150	450	300
mm/dd/yy	150	300	150

424

425 If there is any doubt that there is not enough drug in the Follistim[®] AQ Cartridge for your prescribed
 426 dose, see section 'IF THERE IS NOT ENOUGH FOLLISTIM[®] AQ IN THE CARTRIDGE'.

427

428 **IF THERE IS NOT ENOUGH FOLLISTIM[®] AQ IN THE CARTRIDGE**

429 If you realize before you inject that you do not have enough drug remaining in your Follistim[®] AQ
 430 Cartridge for your complete dose, proceed to Step 1 (below).

431 **OR**

432 If you have already inserted the needle at the injection site and the Injection Button will not push in
 433 all the way, then there is not enough drug contained in the cartridge. The number in the Dosage
 434 Window will not read "0" – this means that there is not enough drug remaining in the Follistim[®]
 435 AQ Cartridge to complete your dose. In this case, proceed to Step 2 (below).

436

437 **Important:**

- 438 • **When there is not enough drug contained in the Follistim[®] AQ Cartridge to complete your**
 439 **injection, the Dosage Knob will not push in all the way and the number in the Dosage Window**
 440 **will not read "0". If this occurs, proceed with the steps that follow.**

441

442 1. If you realize you do not have enough drug remaining in your Follistim[®] AQ Cartridge, you
 443 have 2 options:

444 Option #1: Remove the Follistim[®] AQ Cartridge as outlined in Steps 19 and 20. Insert a new
 445 cartridge into the Follistim Pen[™] (see Steps 3 and 4). Continue with Steps 5 – 18 for your
 446 injection.

447 Option #2: Dial your dose and inject the remaining content in the Follistim[®] AQ Cartridge. The
448 Dosage Knob Injection Button will not push in all the way and the Dosage Window number will
449 not read “0” but will read the number of units you will need to complete your prescribed dose.
450 Remember to write the number of units needed to complete your dose down. Remove the needle
451 and dispose of it properly as outlined in Steps 17 and 18. Using the Dosage Knob, reset the Dial
452 Window to “0” by turning the Dosage Knob past the 450 IU mark as far as it will turn and push
453 the Injection Button in all the way. Insert a new cartridge into the Follistim Pen[™] and attach a
454 new BD Micro-Fine[™] needle (see Steps 3 – 12). Dial to the number of units you have written
455 down to complete your prescribed dose. Prepare a different injection site and inject the
456 remaining drug to complete your dose (refer to USING THE FOLLISTIM PEN[™] TO GIVE
457 YOURSELF AN INJECTION OF FOLLISTIM[®] AQ CARTRIDGE).

458

459 2. If you have already inserted the needle at the injection site, inject the remaining content in the
460 Follistim[®] AQ Cartridge. The Injection Button will not push in all the way and the number in
461 the Dosage Window will not read “0” but will read the number of units you will need to
462 complete your prescribed dose. Wait 5 seconds before withdrawing the needle from your skin
463 and gently apply pressure to the injection site with an alcohol pad. Dispose the used needle
464 properly as outlined in Steps 17 and 18. Remember to write the number of units needed to
465 complete your dose down. Using the Dosage Knob, reset the Dial Window to “0” by turning the
466 Dosage Knob past the 450 IU mark as far as it will turn and push the Injection Button in all the
467 way. Insert a new cartridge into the Follistim Pen[™] and attach a new BD Micro-Fine[™] needle
468 (see Steps 3 – 12). Dial to the number you have recorded to complete your prescribed dose.
469 Prepare a different injection site and inject the remaining drug to complete your dose (refer to
470 USING THE FOLLISTIM PEN[™] TO GIVE YOURSELF AN INJECTION OF
471 FOLLISTIM[®] AQ CARTRIDGE).

472

473 GENERAL INFORMATION ABOUT THE FOLLISTIM[®] AQ CARTRIDGE

474 **Ingredients in Follistim[®] AQ Cartridge**

475 Follistim[®] AQ Cartridge contains the active ingredient follitropin beta. Other inactive ingredients in
476 the cartridges include: sucrose, sodium citrate, polysorbate, benzyl alcohol, L-methionine, water for
477 injection, hydrochloric acid and/or sodium hydroxide.

478 **Caring for the Follistim Pen[™]**

- 479 1. Clean all exposed surfaces of the Follistim Pen[™] with a clean, damp cloth such as a paper
480 towel. Never wash it in water, detergent or strong medical cleaners.
- 481 2. Handle the Pen carefully to avoid causing damage. You could damage the Pen by dropping it or
482 handling it roughly.

- 483 3. Keep the Pen away from dust and dirt.
484 4. If the Pen breaks, do not try to fix it yourself. Contact your doctor.
485 5. Do not share your Follistim Pen™ with another person.

486 **Storing the Follistim Pen™**

- 487 1. Store refrigerated, 2-8°C (36-46°F) until dispensed. Do not freeze. Upon dispensing, the
488 product may be stored by the patient at 2-8°C (36-46°F) until the expiration date, or at 25°C
489 (77°F) for 3 months or until the expiration date, whichever occurs first. Once the rubber stopper
490 of the Follistim® AQ Cartridge has been pierced by a needle, the product may be stored only for
491 a maximum of 28 days at 2-25 °C (36-77 °F).

492 For proper storage of unused Follistim® AQ Cartridges, please see the package insert enclosed
493 with Follistim® AQ Cartridges.

- 494 2. Follistim Pen™ with a Follistim® AQ Cartridge should be protected from light.
495 3. Do not use past the indicated expiration date on the Follistim® AQ Cartridge.
496 4. Keep the Follistim Pen™ containing a Follistim® AQ Cartridge out of the reach and sight of
497 children.
498 5. After your treatment is finished, store the Follistim Pen™ device as instructed by your
499 healthcare professional.

500 **PRECAUTIONS**

- 501 • **Do not share your Follistim Pen™ with another person.**
502 • **The Follistim Pen™ is not recommended for the blind or visually impaired user without**
503 **the assistance of an individual with good vision, trained in the proper use of the device.**
504 • **The Follistim Pen™ is only indicated for use with a Follistim® AQ Cartridge when**
505 **prescribed for subcutaneous injection.**

506 **Care while using the BD Micro-Fine™ Pen Needle**

- 507 • Only attach the BD Micro-Fine™ Pen Needle when you are ready to inject. Always remove the
508 needle from the Follistim Pen™ immediately and dispose of it properly in its Outer Needle
509 Shield after you complete your injection.
510 • The Pen Needle Unit is sterile. To avoid contaminating the needle after opening, do not place it
511 on any surface or touch exposed parts.
512 • Before attempting to replace a Follistim® AQ Cartridge, be sure that a BD Micro-Fine™ Pen
513 Needle is not attached to the Follistim Pen™.
514 • Never dial your dose or attempt to correct a dialing error with the needle in your skin, as this
515 may result in an incorrect dose.

516 • Proper procedures should be used for the disposal of the used needles (fixed in the Outer Needle
517 Shield), “empty” cartridges, and leftover medication. Consult your healthcare professional on
518 the proper procedures for disposal.

519 • The Follistim Pen™ is intended for self-injection of Follistim® AQ Cartridge. If you are giving
520 an injection to another person, be very careful when removing the needle from the skin.
521 Accidental needle sticks can transmit infectious diseases.

522

523 While this leaflet summarizes important information about Follistim® AQ Cartridge, it
524 does not contain all of the possible precautions, side effects, warnings, contraindications, and
525 interactions that may be associated with your drug treatments. Your healthcare provider should
526 discuss your treatment and possible side effects with you. If you would like more information,
527 talk to your doctor. You can ask your pharmacist or doctor for information about Follistim® AQ
528 Cartridge that is written for healthcare providers.

529

For questions on information contained in this leaflet, call

530

1-866-836-5633

531

www.follistim.com

Follistim AQ Cartridge 300 IU
(Follitropin AQ)

One sterile pre-filled cartridge containing 300 IU of Follitropin AQ is available as a delivery device (300 IU).
In active ingredients Benzylalcohol (0.9 mg/mL), L-histidine (0.5 mg/mL), poly sorbate 20 (0.2 mg/mL), sodium chloride (9 mg/mL), sodium citrate (5 mg/mL), zinc sulfate (0.1 mg/mL), hydrochloric acid and sodium hydroxide (0.1 mg/mL) added to adjust pH to 7.

Storage: Store at room temperature (20°-25°/68°-77°F) until dispensed. Upon all pairing the product may be stored by the patient at 2-8°C (36°-46°F) until the expiration date (or at 25°/77°F) for 3 months. Do not use after the expiration date. Once the rubber stopper of the cartridge has been elevated, the product can only be used for a maximum of 10 days (12/24°C/68°/77°F).
Protect from light and moisture.

Do not use if the seal is broken or if the product is cloudy.

For more information call 1-800-XXX-XXXX or visit www.follistim.com



Manufactured and distributed by Eli Lilly and Company, Inc.
Eli Lilly and Company, Inc. 1300 North Dearborn Street
Greenfield, Indiana 46160-1339
© 2013 Eli Lilly and Company. All rights reserved.

HH

Follistim AQ Cartridge 300 IU

(Follitropin AQ Injection)

NDC 0052-0313-01

1 Sterile Follistim AQ Cartridge containing 0.325 mL and 300 IU of Follitropin AQ in 1 Pre-filled Cartridge

Follistim AQ Cartridge 300 IU

(Follitropin AQ Injection)

For use only with Follistim Pen™, available separately

For Subcutaneous Use



U.S. only

236091001 USA 11/13

Lot:

Exp:



Follistim AQ Cartridge 300 IU
(Follitropin AQ)

Follistim Pen™

For use only with
Follistim AQ Cartridge, available separately
(Follistim beta injection)

For more information, call 1-8XX-XXX-XXXX
or visit www.follistim.com

BD is a trademark of Becton Dickinson and Company



Organon USA Inc.
West Orange, NJ 07062

5315391 2/04 30

©2004 Organon USA Inc.

Lot:

Exp:

For use only with
Follistim AQ Cartridge, available separately
BD

Follistim Pen™

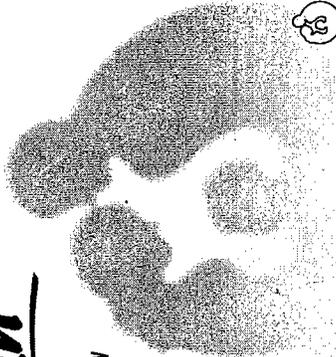
For use only with
Follistim AQ Cartridge, available separately
BD

Follistim Pen™

For use only with
Follistim AQ Cartridge, available separately
(Follistim beta injection)



Contents: 1 Follistim Pen™, 4 BD Micro-Fine™ Pen Needles and
Follistim Pen™ Instructions for Use Manual/Treatment Diary
contained in a Follistim Pen™ Organizer Case
Ⓢ only NOT FOR SALE



MDR 0162-4613-01

Sterile, Prefilled Cartridge
containing 0.25 mL

Rollitin[®] AQ Cartridge 300 IU

(Morphine Mesylate)

Rx only For Subcutaneous Use

Storage: Store refrigerated, 2-8°C (36-46°F), and dispensed. Upon dis-
pensing, the product may be stored by the patient at 2-8°C (36-46°F) until
the expiration date. Do not store at room temperature. Do not use after the
expiration date. If the seal is broken, do not use. Do not freeze. Do not freeze
which ever occurs first. Protect from light. Do not freeze. 5308979 2/04 05

Lot:

Exp:

52642240

MD 0052-0119-01 Sterile Pre-filled Cartridge
Professional Sample — Not For Sale
Part No. 0025-01

Follistim® AQ Cartridge 300 IU

(Morphogen Activity) For Subcutaneous Use

Storage: Store refrigerated, 2-8°C (36-46°F) until dispensed. Upon dis-
pensing, the product may be stored by the patient at 2-8°C (36-46°F) until
the expiration date. Do not freeze. Do not shake. Do not use after expiration date,
whichever occurs first. Protect from light. Do not freeze.

Mfg. for Organon USA Inc., W. Orange, NJ 07062 5309883 2/04 10

Lot:

Exp:

5265240

MSD 0825 0916 01 Sterile Multi-dose Cartridge
Professional Sample — Not For Sale
Product of the United States

Follistim® AQ Cartridge **600 IU**
(Methylnorethynol)

For Subcutaneous Use

Storage: Store refrigerated, 2-8°C (36-46°F) until dispensed. Upon dis-
pensing, the product may be stored by the patient at 2-8°C (36-46°F) until
whichever occurs first: 1) 30 days after the date of dispensing or 2) the
expiration date. Protect from light. Do not freeze. 5308903 2/04 04

MSD, the Organon USA Inc., W. Orange, NJ 07052

Lot:

Exp:

5607240

For use only with
Follistim[®] AQ Cartridge

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daniel A. Shames
3/23/04 05:26:30 PM