

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-149**

**FINAL PRINTED LABELING**

**1 Ovidrel®****2 (choriogonadotropin alfa for injection)****3 FOR SUBCUTANEOUS USE****4 DESCRIPTION**

5 Ovidrel® (choriogonadotropin alfa for injection) is a sterile lyophilized powder composed of  
6 choriogonadotropin alfa (recombinant human Chorionic Gonadotropin, r-hCG), sucrose and  
7 phosphoric acid. The drug substance is produced by recombinant DNA techniques.  
8 Choriogonadotropin alfa is a water soluble glycoprotein consisting of two non-covalently  
9 linked subunits - designated  $\alpha$  and  $\beta$  - consisting of 92 and 145 amino acid residues,  
10 respectively, with carbohydrate moieties linked to ASN-52 and ASN-78 (on alpha subunit)  
11 and ASN-13, ASN-30, SER-121, SER-127, SER-132 and SER-138 (on beta subunit). The  
12 primary structure of the  $\alpha$  - chain of r-hCG is identical to that of the  $\alpha$  - chain of hCG, FSH  
13 and LH. The glycoform pattern of the  $\alpha$  - subunit of r-hCG is closely comparable to urinary  
14 derived hCG (u-hCG), the differences mainly being due to the branching and sialylation  
15 extent of the oligosaccharides. The  $\beta$  - chain has both O- and N-glycosylation sites and its  
16 structure and glycosylation pattern are also very similar to that of u-hCG.

17 The production process involves expansion of genetically modified Chinese Hamster Ovary  
18 (CHO) cells from an extensively characterized cell bank into large scale cell culture  
19 processing. Choriogonadotropin alfa is secreted by the CHO cells directly into the cell  
20 culture medium that is then purified using a series of chromatographic steps. This process  
21 yields a product with a high level of purity and consistent product characteristics including  
22 glycoforms and biological activity. The biological activity of choriogonadotropin alfa is  
23 determined using the seminal vesicle weight gain test in male rats described in the  
24 "Chorionic Gonadotrophins" monograph of the European Pharmacopoeia. The in vivo  
25 biological activity of choriogonadotropin alfa has been calibrated against the third  
26 international reference preparation IS75/587 for chorionic gonadotropin.

27 Ovidrel<sup>®</sup> is a sterile, lyophilized powder intended for subcutaneous (SC) injection after  
28 reconstitution with Sterile Water for Injection, USP. Each vial of Ovidrel<sup>®</sup> contains 285  
29 mcg of choriogonadotropin alfa, 30 mg Sucrose, 0.98 mg Phosphoric acid, and Sodium  
30 Hydroxide (for pH adjustment) which, when reconstituted with the diluent, will deliver 250  
31 mcg of recombinant human Chorionic Gonadotropin. The pH of reconstituted solution is 6.5  
32 to 7.5.

33 Therapeutic Class: Infertility

#### 34 **CLINICAL PHARMACOLOGY**

35 The physicochemical, immunological, and biological activities of recombinant hCG are  
36 comparable to those of placental and human pregnancy urine-derived hCG.

37 Choriogonadotropin alfa stimulates late follicular maturation and resumption of oocyte  
38 meiosis, and initiates rupture of the pre-ovulatory ovarian follicle. Choriogonadotropin alfa,  
39 the active component of Ovidrel®, is an analogue of Luteinizing Hormone (LH) and binds to  
40 the LH/hCG receptor of the granulosa and theca cells of the ovary to effect these changes in  
41 the absence of an endogenous LH surge. In pregnancy, hCG, secreted by the placenta,  
42 maintains the viability of the corpus luteum to provide the continued secretion of estrogen  
43 and progesterone necessary to support the first trimester of pregnancy. Ovidrel® is  
44 administered when monitoring of the patient indicates that sufficient follicular development  
45 has occurred in response to FSH treatment for ovulation induction.

#### 46 **Pharmacokinetics**

47 When given by intravenous administration, the pharmacokinetic profile of Ovidrel®  
48 followed a biexponential model and was linear over a range of 25 mcg to 1000 mcg.  
49 Pharmacokinetic parameter estimates following SC administration of Ovidrel® 250 mcg to  
50 females are presented in Table 1.

51 **Table 1: Pharmacokinetic Parameters (mean ± SD) of r-hCG after Single-Dose**  
52 **Administration of Ovidrel® in Healthy Female Volunteers**

	Ovidrel® 250 mcg SC
$C_{max}$ (IU/L)	121 ± 44
$t_{max}$ (h)*	24 (12-24)
AUC (h·IU/L)	7701 ± 2101
$t_{1/2}$ (h)	29 ± 6
F	0.4 ± 0.1

53  $C_{max}$ : peak concentration (above baseline),  $t_{max}$ : time of  $C_{max}$ , AUC: total area under the curve,  $t_{1/2}$ : elimination half-life, F: bioavailability  
54 \* median (range)

### 55 Absorption

56 Following subcutaneous administration of Ovidrel® 250 mcg, maximum serum concentration  
57 (121 ± 44 IU/L) is reached after approximately 12 to 24 hours. The mean absolute  
58 bioavailability of Ovidrel® following a single subcutaneous injection to healthy female  
59 volunteers is about 40%.

### 60 Distribution

61 Following intravenous administration of Ovidrel® 250 mcg to healthy down-regulated  
62 female volunteers, the serum profile of hCG is described by a two-compartment model with  
63 an initial half-life of 4.5 ± 0.5 hours. The volume of the central compartment is 3.0 ± 0.5 L  
64 and the steady state volume of distribution is 5.9 ± 1.0 L.

65 Metabolism/Excretion

66 Following subcutaneous administration of Ovidrel®, hCG is eliminated from the body with a  
67 mean terminal half-life of about  $29 \pm 6$  hours. After intravenous administration of Ovidrel®  
68 250 mcg to healthy down-regulated females, the mean terminal half-life is  $26.5 \pm 2.5$  hours  
69 and the total body clearance is  $0.29 \pm 0.04$  L/h. One-tenth of the dose is excreted in the  
70 urine.

71 Pharmacodynamics

72 In female subjects on oral contraception after an initial latency period, Ovidrel® induced a  
73 clear increase in androstenedione serum levels by 24 hours after dosing. Pharmacodynamic  
74 studies in females determined that the relationship of Ovidrel® pharmacokinetics to  
75 pharmacologic effect of Ovidrel® are complex and vary with the pharmacodynamic marker  
76 examined. In general pharmacologic effects are not proportional to exposure and in some  
77 cases appear to be near maximal at a 250 mcg dose.

78 Population pharmacokinetics and pharmacodynamics

79 In patients undergoing *in-vitro* fertilization/embryo transfer given Ovidrel® subcutaneously to  
80 trigger ovulation, the results of a population PK/PD analysis generally supported the data  
81 obtained in healthy subjects. Pharmacokinetic parameters for Ovidrel® include a median  
82 elimination half-life of 29.2 hours, median apparent clearance (Cl/F) of 0.51 L/hr and median  
83 apparent volume of distribution (V/F) of 21.4 L.

84 **Special populations:** Safety, efficacy, and pharmacokinetics of Ovidrel® in patients with  
85 renal or hepatic insufficiency have not been established.

86 **Drug-Drug Interactions:** No drug-drug interaction studies have been conducted.  
87 Administration of Ovidrel® may interfere with the interpretation of pregnancy tests. (see  
88 PRECAUTIONS.)

89 **Clinical Studies:**

90 The safety and efficacy of Ovidrel® have been examined in three well-controlled studies in  
91 women; two studies for assisted reproductive technologies (ART) and one study for  
92 ovulation induction (OI).

93 **Assisted Reproductive Technologies (ART)**

94 The safety and efficacy of Ovidrel® 250 mcg and Ovidrel® 500 mcg administered  
95 subcutaneously versus 10,000 USP Units of an approved urinary-derived hCG product  
96 administered intramuscularly were assessed in a randomized, open-label, multicenter study in  
97 infertile women undergoing *in vitro* fertilization and embryo transfer (Study 7927). The  
98 study was conducted in 20 U.S. centers.

99 The primary efficacy parameter in this single-cycle study was the number of oocytes  
100 retrieved. 297 patients entered the study, of whom 94 were randomized to receive Ovidrel®  
101 250 mcg. The number of oocytes retrieved was similar for the Ovidrel® and urinary-derived  
102 hCG (10,000 USP Units) treatment groups. The efficacy of Ovidrel® 250 mcg and Ovidrel®

103 500 mcg were both found to be clinically and statistically equivalent to that of the approved  
 104 urinary-derived hCG product and to each other. The efficacy results for the patients who  
 105 received Ovidrel® 250 mcg are summarized in Table 2.

106 **Table 2: Efficacy Outcomes of r-hCG in ART (Study 7927)**

Parameter	Ovidrel® 250 mcg (n = 94)
Mean number of oocytes retrieved per patient	13.60
Mean number of mature oocytes retrieved per patient	7.6
Mean number of 2 PN fertilized oocytes per patient	7.2
Mean number of 2 PN or cleaved embryos per patient	7.6
Implantation rate per embryo transferred (%)	18.7
Mean mid-luteal serum progesterone levels (nmol/L*)	423
Clinical pregnancy rate per initiated treatment cycle (%) <sup>□</sup>	35.1
Clinical pregnancy rate per transfer (%) <sup>□</sup>	36.3

107 <sup>□</sup>Clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heartbeat activity)  
 108 was detected by ultrasound on day 35-42 after hCG administration)  
 109 \*nmol/L ÷ 3.18 = ng/mL

110 For the 33 patients who achieved a clinical pregnancy with Ovidrel® 250 mcg, the outcomes  
 111 of the pregnancies are presented in Table 3.

112 **Table 3: Pregnancy Outcomes of r-hCG in ART (Study 7927)**

Parameter	Ovidrel® 250 mcg (n = 33)
Clinical pregnancies not reaching term	4 (12.1%)
Live births	29 (87.9%)
<i>Singleton</i>	20 (69.0%)
<i>Multiple birth</i>	9 (31.0%)

113 The safety and efficacy of Ovidrel® 250 mcg administered subcutaneously versus 5,000 IU of  
114 an approved urinary-derived hCG product administered subcutaneously were assessed in a  
115 second, randomized, multicenter study in infertile women undergoing *in vitro* fertilization  
116 and embryo transfer (Study 7648). This double-blinded study was conducted in nine centers  
117 in Europe and Israel.

118 The primary efficacy parameter in this single-cycle study was the number of oocytes  
119 retrieved per patient. 205 patients entered the study, of whom 97 received Ovidrel® 250  
120 mcg. The efficacy of Ovidrel® 250 mcg was found to be clinically and statistically  
121 equivalent to that of the approved urinary-derived hCG product. The results for the 97  
122 patients who received Ovidrel® 250 mcg are summarized in Table 4.

123 **Table 4: Efficacy Outcomes of r-hCG in ART (Study 7648)**

Parameter	Ovidrel® 250 mcg (n = 97)
Mean number of oocytes retrieved per patient	10.6
Mean number of mature oocytes retrieved per patient	10.1
Mean number of 2 PN fertilized oocytes per patient	5.7
Mean number of 2 PN or cleaved embryos per patient	5.1
Implantation rate per embryo transferred (%)	17.4
Mean mid-luteal serum progesterone levels (nmol/L)*	394
Clinical pregnancy rate per initiated treatment cycle (%) <sup>□</sup>	33
Clinical pregnancy rate per transfer (%) <sup>□</sup>	37.6

124 <sup>□</sup> Clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heartbeat activity)  
 125 was detected by ultrasound on day 35-42 after hCG administration)

126 \* nmol/L ÷ 3.18 = ng/mL

127 For the 32 patients who achieved a clinical pregnancy with Ovidrel® 250 mcg, the outcomes  
 128 of the pregnancies are presented in Table 5.

129 **Table 5: Pregnancy Outcomes of r-hCG in ART (Study 7648)**

Parameter	Ovidrel® 250 mcg
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	(n = 32)
Clinical Pregnancies not reaching term	6 (18.8%)
Live births	26 (81.2%)
<i>Singleton</i>	18 (69.2%)
<i>Multiple birth</i>	8 (30.8%)

130 **Ovulation Induction (OI)**

131 The safety and efficacy of Ovidrel® 250 mcg administered subcutaneously versus 5,000 IU of  
132 an approved urinary-derived hCG product administered intramuscularly were assessed in a  
133 double-blind, randomized, multicenter study in anovulatory infertile women (Study 8209)  
134 which was conducted in 19 centers in Australia, Canada, Europe and Israel.

135 The primary efficacy parameter in this single-cycle study was the patient ovulation rate. 242  
136 patients entered the study, of whom 99 received Ovidrel® 250 mcg. The efficacy of Ovidrel®  
137 250 mcg was found to be clinically and statistically equivalent to that of the approved  
138 urinary-derived hCG product. The results of those patients who received Ovidrel® 250 mcg  
139 are summarized in Table 6.

140 **Table 6: Efficacy Outcomes of r-hCG in OI (Study 8209)**

Parameter	Ovidrel® 250 mcg (n = 99)
Ovulation Rate	91 (91.9%)
Clinical Pregnancy Rate <sup>†</sup>	22 (22%)

141 <sup>†</sup>Clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heartbeat activity) was detected  
 142 by ultrasound on day 35-42 after hCG administration.

143 For the 22 patients who had a clinical pregnancy with Ovidrel® 250 mcg, the outcome of the  
 144 pregnancy is presented in Table 7.

145 **Table 7: Pregnancy Outcomes of r-hCG in OI (Study 8209)**

Parameter	Ovidrel® 250 mcg (n = 22)
Clinical pregnancies not reaching term	7 (31.8%)
Live births	15 (68.2%)
<i>Singleton</i>	<i>13 (86.7%)</i>
<i>Multiple birth</i>	<i>2 (13.3%)</i>

**146 INDICATIONS AND USAGE**

147 Ovidrel® (choriogonadotropin alfa for injection) is indicated for the induction of final  
148 follicular maturation and early luteinization in infertile women who have undergone pituitary  
149 desensitization and who have been appropriately pretreated with follicle stimulating  
150 hormones as part of an Assisted Reproductive Technology (ART) program such as *in vitro*  
151 fertilization and embryo transfer. Ovidrel® is also indicated for the induction of ovulation  
152 (OI) and pregnancy in anovulatory infertile patients in whom the cause of infertility is  
153 functional and not due to primary ovarian failure.

**154 Selection of Patients:**

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

**166 CONTRAINDICATIONS**

167 Ovidrel® (choriogonadotropin alfa for injection) is contraindicated in women who exhibit:

- 168 1. Prior hypersensitivity to hCG preparations or one of their excipients.
- 169 2. Primary ovarian failure.
- 170 3. Uncontrolled thyroid or adrenal dysfunction.
- 171 4. An uncontrolled organic intracranial lesion such as a pituitary tumor.
- 172 5. Abnormal uterine bleeding of undetermined origin (see "Selection of Patients").
- 173 6. Ovarian cyst or enlargement of undetermined origin (see "Selection of Patients").
- 174 7. Sex hormone dependent tumors of the reproductive tract and accessory organs.
- 175 8. Pregnancy.

**176 WARNINGS**

177 Gonadotropins, including Ovidrel® (choriogonadotropin alfa for injection), should only be  
178 used by physicians who are thoroughly familiar with infertility problems and their  
179 management. Like other hCG products, Ovidrel® is a potent gonadotropic substance capable  
180 of causing Ovarian Hyperstimulation Syndrome (OHSS) in women with or without  
181 pulmonary or vascular complications. Gonadotropin therapy requires a certain time  
182 commitment by physicians and supportive health professionals, and requires the availability  
183 of appropriate monitoring facilities (see "Precautions/ Laboratory Tests"). Safe and effective

184 induction of ovulation and use of Ovidrel® in women requires monitoring of ovarian  
185 response with serum estradiol and transvaginal ultrasound on a regular basis.

186 **Overstimulation of the Ovary Following hCG Therapy:**

187 Ovarian Enlargement:

188 Mild to moderate uncomplicated ovarian enlargement which may be accompanied by  
189 abdominal distention and/or abdominal pain may occur in patients treated with FSH and  
190 hCG, and generally regresses without treatment within two or three weeks. Careful  
191 monitoring of ovarian response can further minimize the risk of overstimulation.

192 If the ovaries are abnormally enlarged on the last day of FSH therapy, choriogonadotropin  
193 alfa should not be administered in this course of therapy. This will reduce the risk of  
194 development of Ovarian Hyperstimulation Syndrome.

195 Ovarian Hyperstimulation Syndrome (OHSS):

196 OHSS is a medical event distinct from uncomplicated ovarian enlargement. Severe OHSS  
197 may progress rapidly (within 24 hours to several days) to become a serious medical event. It  
198 is characterized by an apparent dramatic increase in vascular permeability which can result in  
199 a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the  
200 pericardium. The early warning signs of development of OHSS are severe pelvic pain,  
201 nausea, vomiting, and weight gain. The following symptomatology has been seen with cases  
202 of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including  
203 nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and

204 oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte  
205 imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary  
206 distress, and thromboembolic events (see "Pulmonary and Vascular Complications").  
207 Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be  
208 accompanied by morphologic changes on liver biopsy, have been reported in association with  
209 Ovarian Hyperstimulation Syndrome (OHSS).

210 OHSS occurred in 4 of 236 (1.7 %) patients treated with Ovidrel® 250 mcg during clinical  
211 trials for ART and 3 of 99 (3.0%) patients treated in the OI trial. OHSS occurred in 8 of 89  
212 (9.0%) patients who received Ovidrel® 500 mcg. Two patients treated with Ovidrel® 500  
213 mcg developed severe OHSS.

214 OHSS may be more severe and more protracted if pregnancy occurs. OHSS develops  
215 rapidly; therefore, patients should be followed for at least two weeks after hCG  
216 administration. Most often, OHSS occurs after treatment has been discontinued and reaches  
217 its maximum at about seven to ten days following treatment. Usually, OHSS resolves  
218 spontaneously with the onset of menses. If there is evidence that OHSS may be developing  
219 prior to hCG administration (see "Precautions/Laboratory Tests"), the hCG must be withheld.

220 If severe OHSS occurs, treatment with gonadotropins must be stopped and the patient should  
221 be hospitalized.

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

224 **Multiple Births:** As with other hCG products, reports of multiple births have been  
225 associated with Ovidrel® treatment. In ART, the risk of multiple births correlates to the  
226 number of embryos transferred. Multiple births occurred in 17 of 55 live deliveries (30.9 %)  
227 experienced by women receiving Ovidrel® 250 mcg in the ART studies. In the ovulation  
228 induction clinical trial, 2 of 15 live deliveries (13.3%) were associated with multiple births in  
229 women receiving Ovidrel®. The patient should be advised of the potential risk of multiple  
230 births before starting treatment.

231 **Pulmonary and Vascular Complications:** As with other hCG products, a potential for the  
232 occurrence of arterial thromboembolism exists.

### 233 **PRECAUTIONS**

234 **General:** Careful attention should be given to the diagnosis of infertility in candidates for  
235 hCG therapy. (see "Indications and Usage/ Selection of Patients"). After the exclusion of  
236 pre-existing conditions, elevations in ALT were found in 10 (3%) of 335 patients receiving  
237 Ovidrel® 250 mcg, 9 (10%) of 89 patients receiving Ovidrel® 500 mcg and in 16 (4.8%) of  
238 328 patients receiving urinary-derived hCG. The elevations ranged up to 1.2 times the upper  
239 limit of normal. The clinical significance of these findings is not known.

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

244 **Laboratory Tests:** In most instances, treatment of women with FSH results only in  
245 follicular recruitment and development. In the absence of an endogenous LH surge, hCG is  
246 given when monitoring of the patient indicates that sufficient follicular development has  
247 occurred. This may be estimated by ultrasound alone or in combination with measurement of  
248 serum estradiol levels. The combination of both ultrasound and serum estradiol  
249 measurement are useful for monitoring the development of follicles, for timing of the  
250 ovulatory trigger, as well as for detecting ovarian enlargement and minimizing the risk of the  
251 Ovarian Hyperstimulation Syndrome and multiple gestation. It is recommended that the  
252 number of growing follicles be confirmed using ultrasonography because serum estrogens do  
253 not give an indication of the size or number of follicles.

254 Human chorionic gonadotropins can crossreact in the radioimmunoassay of gonadotropins,  
255 especially luteinizing hormone. Each individual laboratory should establish the degree of  
256 crossreactivity with their gonadotropin assay. Physicians should make the laboratory aware  
257 of patients on hCG if gonadotropin levels are requested.

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

- 261 1. A rise in basal body temperature
- 262 2. Increase in serum progesterone and
- 263 3. Menstruation following a shift in basal body temperature

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

- 267 1. Fluid in the cul-de-sac
- 268 2. Ovarian stigmata
- 269 3. Collapsed follicle
- 270 4. Secretory endometrium

271 Accurate interpretation of the indices of ovulation require a physician who is experienced in  
272 the interpretation of these tests.

273 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies to evaluate the  
274 carcinogenic potential of Ovidrel® in animals have not been performed. In-vitro genotoxicity  
275 testing of Ovidrel® in bacteria and mammalian cell lines, chromosome aberration assay in  
276 human lymphocytes and in-vivo mouse micronucleus have shown no indication of genetic  
277 defects.

278 **Pregnancy:** Pregnancy Category X. Fetal death and impaired parturition were observed in  
279 pregnant rats given a dose of choriogonadotropin alfa (25 mcg/day) equivalent to six times  
280 the maximum human dose of 250 mcg based on body surface area.

281 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because  
282 many drugs are excreted in human milk, caution should be exercised if hCG is administered  
283 to a nursing woman.

284 **Pediatric Patients:** Safety and effectiveness in pediatric patients has not been established.

285 **Geriatric Patients:** Safety and effectiveness in geriatric patients has not been established.

## 286 **ADVERSE REACTIONS**

287 (see WARNINGS)

288 The safety of Ovidrel® was examined in four clinical studies that treated 752 patients of  
289 whom 335 received Ovidrel® 250 mcg following follicular recruitment with gonadotropins.  
290 When patients enrolled in four clinical studies (3 in ART and one in OI) were injected  
291 subcutaneously with either Ovidrel® or an approved urinary-derived hCG, 14.6 % (49 of 335  
292 patients) in the Ovidrel® 250mcg group experienced application site disorders compared to  
293 28% (92 of 328 patients) in the approved u-hCG group. Adverse events reported for  
294 Ovidrel® 250 mcg occurring in at least 2% of patients (regardless of causality) are listed in  
295 Table 8 for the 3 ART studies and in Table 9 for the single OI study.

296 **Table 8: Incidence of Adverse Events of r-hCG in ART (Studies 7648, 7927, 9073)**

Body System Preferred Term	Ovidrel® 250 mcg (n=236) Incidence Rate % (n)
At Least One Adverse Event	33.1% (78)
APPLICATION SITE DISORDERS	14.0% (33)
INJECTION SITE PAIN	7.6% (18)
INJECTION SITE BRUISING	4.7% (11)
GASTRO-INTESTINAL SYSTEM DISORDERS	8.5% (20)
ABDOMINAL PAIN	4.2% (10)
NAUSEA	3.4% ( 8)
VOMITING	2.5% ( 6)
SECONDARY TERMS (POST-OPERATIVE PAIN)	4.7% (11)
POST-OPERATIVE PAIN	4.7% (11)

297 Adverse events not listed in Table 8 that occurred in less than 2% of patients treated with  
 298 Ovidrel® 250 mcg whether or not considered causally related to Ovidrel®, included:  
 299 injection site inflammation and reaction, flatulence, diarrhea, hiccup, ectopic pregnancy,  
 300 breast pain, intermenstrual bleeding, vaginal hemorrhage, cervical lesion, leukorrhea, ovarian  
 301 hyperstimulation, uterine disorders, vaginitis, vaginal discomfort, body pain, back pain,  
 302 fever, dizziness, headache, hot flashes, malaise, paraesthesias, rash, emotional lability,  
 303 insomnia, upper respiratory tract infection, cough, dysuria, urinary tract infection, urinary  
 304 incontinence, albuminuria, cardiac arrhythmia, genital moniliasis, genital herpes,  
 305 leukocytosis, heart murmur and cervical carcinoma.

306 **Table 9: Incidence of Adverse Events of r-hCG in Ovulation Induction (Study 8209)**

Body System Preferred Term	Ovidrel® 250 mcg (n=99) Incidence Rate % (n)
At Least One Adverse Event	26.2% (26)
APPLICATION SITE DISORDERS	16.2% (16)
INJECTION SITE PAIN	8.1% (8)
INJECTION SITE INFLAMMATION	2.0% (2)
INJECTION SITE BRUISING	3.0% (3)
INJECTION SITE REACTION	3.0% (3)
REPRODUCTIVE DISORDERS, FEMALE	7.1% (7)
OVARIAN CYST	3.0% (3)
OVARIAN HYPERSTIMULATION	3.0% (3)
GASTRO—INTESTINAL SYSTEM DISORDERS	4.0% (4)
ABDOMINAL PAIN	3.0% (3)

307 Additional adverse events not listed in Table 9 that occurred in less than 2% of patients  
308 treated with Ovidrel® 250 mcg, whether or not considered causally related to Ovidrel®,  
309 included: breast pain, flatulence, abdominal enlargement, pharyngitis, upper respiratory tract  
310 infection, hyperglycemia and pruritis.

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

- 313 1. Spontaneous Abortion
- 314 2. Ectopic Pregnancy
- 315 3. Premature Labor

- 316 4. Postpartum Fever  
317 5. Congenital abnormalities

318 Of 125 clinical pregnancies reported following treatment with FSH and Ovidrel® 250 mcg or  
319 500 mcg, three were associated with a congenital anomaly of the fetus or newborn. Among  
320 patients receiving Ovidrel® 250 mcg, cranial malformation was detected in the fetus of one  
321 woman and a chromosomal abnormality (47, XXX) in another. These events were judged by  
322 the investigators to be of unlikely or unknown relation to treatment. These three events  
323 represent an incidence of major congenital malformations of 2.4%, which is consistent with  
324 the reported rate for pregnancies resulting from natural or assisted conception. In a woman  
325 who received Ovidrel® 500 mcg, one birth in a set of triplets was associated with Down's  
326 syndrome and atrial septal defect. This event was considered to be unrelated to the study  
327 drug.

328 The following adverse reactions have been previously reported during menotropin therapy:

- 329 1. Pulmonary and vascular complications (see "Warnings")  
330 2. Adnexal torsion (as a complication of ovarian enlargement)  
331 3. Mild to moderate ovarian enlargement  
332 4. Hemoperitoneum

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

336 **DOSAGE AND ADMINISTRATION**

337 *For Subcutaneous Use Only*

338 **Infertile Women Undergoing Assisted Reproductive Technologies (ART)**

339 Ovidrel® 250 mcg should be administered one day following the last dose of the follicle  
340 stimulating agent. Ovidrel® should not be administered until adequate follicular development  
341 is indicated by serum estradiol and vaginal ultrasonography. Administration should be  
342 withheld in situations where there is an excessive ovarian response, as evidenced by  
343 clinically significant ovarian enlargement or excessive estradiol production.

344 **Infertile Women Undergoing Ovulation Induction (OI)**

345 Ovidrel® should not be administered until adequate follicular development is indicated by  
346 serum estradiol and vaginal ultrasonography.

347 Ovidrel® 250 mcg should be administered one day following the last dose of the follicle  
348 stimulating agent.

349 Ovidrel® administration should be withheld in situations where there is an excessive ovarian  
350 response, as evidenced by multiple follicular development, clinically significant ovarian  
351 enlargement or excessive estradiol production.

352 **Directions for Administration of Ovidrel®:**

353 Ovidrel® is intended for a single subcutaneous injection and should be administered  
354 following reconstitution with 1 mL of Sterile Water for Injection. Any unused reconstituted  
355 material should be discarded.

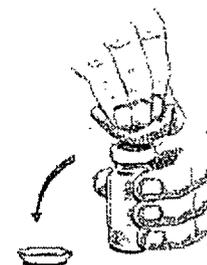
356 Ovidrel® may be self-administered by the patient. Follow the directions below for  
357 reconstituting (mixing) and injecting Ovidrel®.

358 **Step 1: Wash your hands thoroughly with soap and water. Remove the plastic flip-tops**  
359 **from both vials.**

360 After removing the plastic flip-tops with your thumb, wipe the rubber stoppers with alcohol.  
361 The rubber stoppers should not be touched after they are wiped.

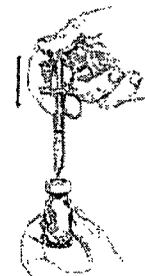
362 **Step 2: Carefully remove the needle cover. Do not touch the needle or allow the needle**  
363 **to touch any surface.**

364 After removing the needle cover, draw air into the syringe by slowly pulling back the plunger  
365 to the 1 cc mark. Carefully insert the needle through the rubber stopper into the vial with the  
366 sterile water (diluent). Gently inject the air into the vial (the injected air creates pressure,  
367 which makes withdrawing the liquid easier). Without withdrawing the needle, turn the vial  
368 upside down and withdraw all of the water into the syringe, making sure the tip of the needle  
369 remains in the water. Withdraw the needle from the vial.



370 **Step 3: Insert the needle through the rubber stopper into the vial containing the**  
371 **powdered Ovidrel®.**

372 Keep the syringe in a straight, upright position as you insert it through the center of the  
373 rubber stopper, or it may be difficult to depress the plunger. After inserting the needle,  
374 slowly inject the sterile water (diluent) toward the side of the vial of powdered Ovidrel®  
375 (choriogonadotropin alfa for injection).



376 **Step 4: Leaving the needle in the vial, gently rotate the vial. Do not shake.**

377 Gently mix by rotating the vial between your fingers until all of the powder is fully  
378 dissolved.



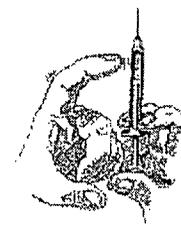
379 **Step 5: Withdraw the liquid from the vial.**

380 The solution should not be withdrawn for use if it is not clear and colorless. Without  
381 withdrawing the needle, turn the vial upside down and withdraw all of the reconstituted  
382 Ovidrel® into the syringe (again, make sure the tip of the needle remains in the solution). It is  
383 necessary to slowly back the needle out of the vial to withdraw as much of the liquid solution  
384 as possible. Next, withdraw the needle from the vial.



385 **Step 6: Remove any bubbles in the syringe.**

386 To remove any air bubbles in the syringe, point the needle up and tap the syringe. When all  
387 the bubbles float to the top, slightly push the plunger until a small drop or two of liquid  
388 begins to appear from the tip of the needle. Now you are ready to inject Ovidrel®.



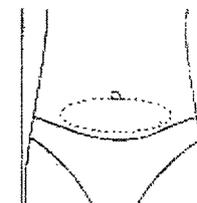
389 **Step 7: Recap the syringe needle.**

390 Recap the syringe needle. Do not touch the needle or allow the needle to touch any surface.

391 Carefully lay the syringe down on a flat, clean surface.

392 **Step 8: Carefully clean the injection site.**

393 Make yourself comfortable by sitting or lying down. Carefully clean the injection site on the  
394 stomach with an alcohol wipe and allow it to air-dry.



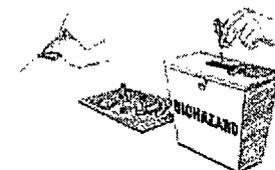
395 **Step 9: Administer your injection.**

396 Carefully remove the needle cap from the syringe. Holding the syringe in one hand, use your  
397 other hand to gently grasp a fold of skin. Hold the syringe the way you would hold a pencil  
398 and, with a smooth, dart-like motion, insert the needle at a slight angle into the injection site.  
399 Pull back the plunger slightly. When the needle is correctly positioned, it will be difficult to  
400 pull back on the plunger. If any blood is drawn into the syringe, the needle tip has penetrated  
401 a vein or artery. If this happens, withdraw the needle slightly and reposition the needle  
402 without removing it from the skin. Alternatively, remove the needle, reconstitute and use a  
403 new solution (as previously discussed). Once the needle is correctly placed, push the plunger  
404 in a slow, steady motion until all the medication is injected. Then, release the skin.



405 **Step 10: Gently withdraw the needle.**

406 Discard the needle and syringe into your safety container. Place gauze over the injection site.  
407 If any bleeding occurs, apply gentle pressure. If bleeding does not stop within a few minutes,  
408 place a clean piece of gauze over the injection site and cover it with an adhesive bandage.



409 **Step 11: Storage and clean up.**

410 Remember that your injection materials must be kept sterile and cannot be reused.

411 **HOW SUPPLIED**

412 Ovidrel® (choriogonadotropin alfa for injection) is supplied in sterile, lyophilized single dose  
413 vial containing 285 mcg r-hCG to deliver 250 mcg r-hCG, after reconstitution with the  
414 diluent.

415 The following package combinations is available:

416 - 1 vial 250 mcg Ovidrel® and 1 vial 1 mL Sterile Water for Injection, USP,

417 NDC 44087-0250-1

418 Storage: Vials may be stored refrigerated or at room temperature (2°-25° C / 36°-77° F)

419 Protect from light.

420 Store in original package. Use immediately after reconstitution. Discard unused material.

421 **Rx Only**

422 Distributed by: Serono, Inc. Randolph, MA 02368

423 *Draft September 20, 2000*