OVIDREL - choriogonadotropin alfa injection, solution
EMD Serono, Inc.

OVIDREL® PreFilled Syringe
(choriogonadotropin alfa injection)

FOR SUBCUTANEOUS USE

DESCRIPTION

Ovidrel® PreFilled Syringe (choriogonadotropin alfa injection) is a sterile liquid preparation of choriogonadotropin alfa (recombinant human Chorionic Gonadotropin, r-hCG). Choriogonadotropin alfa is a water soluble glycoprotein consisting of two non-covalently linked subunits - designated α and β - consisting of 92 and 145 amino acid residues, respectively, with carbohydrate moieties linked to ASN-52 and ASN-78 (on alpha subunit) and ASN-13, ASN-30, SER-121, SER-127, SER-132 and SER-138 (on beta subunit). The primary structure of the α - chain of r-hCG is identical to that of the α - chain of hCG, FSH and LH. The glycoform pattern of the α - subunit of r-hCG is closely comparable to urinary derived hCG (u-hCG), the differences mainly being due to the branching and sialylation extent of the oligosaccharides. The β - chain has both O- and N-glycosylation sites and its structure and glycosylation pattern are also very similar to that of u-hCG.

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

Ovidrel® PreFilled Syringe is a sterile, liquid intended for subcutaneous (SC) injection. Each Ovidrel® PreFilled Syringe is filled with 0.515 mL containing 257.5 µg of choriogonadotropin alfa, 28.1 mg mannitol, 505 µg 85% O-phosphoric acid, 103 µg L-methionine, 51.5 µg Poloxamer 188, Sodium Hydroxide (for pH adjustment), and Water for Injection to deliver 250 µg of choriogonadotropin alfa in 0.5 mL. The pH of the solution is 6.5 to 7.5.

Therapeutic Class: Infertility

CLINICAL PHARMACOLOGY

The physicochemical, immunological, and biological activities of recombinant hCG are comparable to those of placental and human pregnancy urine-derived hCG. Choriogonadotropin alfa stimulates late follicular maturation and resumption of oocyte meiosis, and initiates rupture of the pre-ovulatory ovarian follicle. Choriogonadotropin alfa, the active component of Ovidrel® PreFilled Syringe , is an analogue of Luteinizing Hormone (LH) and binds to the LH/hCG receptor of the granulosa and theca cells of the ovary to effect these changes in the absence of an endogenous LH surge. In pregnancy, hCG, secreted by the placenta, maintains the viability of the corpus luteum to provide the continued secretion of estrogen and progesterone necessary to support the first trimester of pregnancy. Ovidrel® PreFilled Syringe is administered when monitoring of the patient indicates that sufficient follicular development has occurred in response to FSH treatment for ovulation induction.

Pharmacokinetics

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

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

	Ovidrel® 250 µg SC
C_{max} (IU/L)	121 ± 44
t_{max} (h)*	24 (12-24)
AUC (h·IU/L)	7701 ± 2101
$t_{½}$ (h)	29 ± 6
F	0.4 ± 0.1

C_{max}: peak concentration (above baseline), t_{max}: time of C_{max}, AUC: total area under the curve, $t_{½}$: elimination half-life, F: bioavailability

* median (range)

Absorption

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

Distribution

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

Metabolism/Excretion

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

Pharmacodynamics

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

Population pharmacokinetics and pharmacodynamics

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

Bioequivalence of Formulations

Ovidrel® PreFilled Syringe (choriogonadotropin alfa injection) has been determined to be bioequivalent to Ovidrel® (choriogonadotropin alfa for injection) based on the statistical evaluation of AUC and C_{max}. A summary of the Ovidrel® PreFilled Syringe pharmacokinetic parameters is presented in Table 2.

Table 2: Summary of Ovidrel® PreFilled Syringe Pharmacokinetic Parameters

Parameter	C_{max} (mIU/mL)	$AUCl_{ast}$ (mIU·h/mL)	AUC (mIU·h/mL)	$AUC_{extrapolated}$ (%)	t_{max} (h)
Mean	125	10050	10350	2.85	20.0
(Min-Max)	(68.0-294)	(5646-14850)	(5800-15100)	(1.08-6.27)	(9.00-48.0)

Abbreviations are: C_{max}: peak concentration (above baseline); t_{max} : time of C_{max}

Special populations

Safety, efficacy, and pharmacokinetics of Ovidrel® PreFilled Syringe in patients with renal or hepatic insufficiency have not been established.

Drug-Drug Interactions

No drug-drug interaction studies have been conducted. Administration of Ovidrel® PreFilled Syringe may interfere with the interpretation of pregnancy tests. (see PRECAUTIONS.)

CLINICAL STUDIES

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

Assisted Reproductive Technologies (ART)

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

The primary efficacy parameter in this single-cycle study was the number of oocytes retrieved. 297 patients entered the study, of whom 94 were randomized to receive Ovidrel® 250 µg. The number of oocytes retrieved was similar for the Ovidrel® and urinary-derived hCG (10,000 USP Units) treatment groups. The efficacy of Ovidrel® 250 µg and Ovidrel® 500 µg were both found to be clinically and statistically equivalent to that of the approved urinary-derived hCG product and to each other. The efficacy results for the patients who received Ovidrel® 250 µg are summarized in Table 3.

Table 3: Efficacy Outcomes of r-hCG in ART (Study 7927)

Parameter	Ovidrel® 250 µg (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 (%)†	35.1
Clinical pregnancy rate per transfer (%)†	36.3

* nmol/L ÷ 3.18 = ng/mL

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

For the 33 patients who achieved a clinical pregnancy with Ovidrel® 250 µg, the outcomes of the pregnancies are presented in Table 4.

Table 4: Pregnancy Outcomes of r-hCG in ART (Study 7927)

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

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

The primary efficacy parameter in this single-cycle study was the number of oocytes retrieved per patient. 205 patients entered the study, of whom 97 received Ovidrel® 250 µg. The efficacy of Ovidrel® 250 µg was found to be clinically and statistically equivalent to that of the approved urinary-derived hCG product. The results for the 97 patients who received Ovidrel® 250 µg are summarized in Table 5.

Table 5: Efficacy Outcomes of r-hCG in ART (Study 7648)

Parameter	**Ovidrel® 250 µg (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 (%)†	33
Clinical pregnancy rate per transfer (%)†	37.6

* nmol/L ÷ 3.18 = ng/mL

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

For the 32 patients who achieved a clinical pregnancy with Ovidrel® 250 µg, the outcomes of the pregnancies are presented in Table 6.

Table 6: Pregnancy Outcomes of r-hCG in ART (Study 7648)

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

Ovulation Induction (OI)

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

The primary efficacy parameter in this single-cycle study was the patient ovulation rate. 242 patients entered the study, of whom 99 received Ovidrel® 250 µg. The efficacy of Ovidrel® 250 µg was found to be clinically and statistically equivalent to that of the approved urinary-derived hCG product. The results of those patients who received Ovidrel® 250 µg are summarized in Table 7.

Table 7: Efficacy Outcomes of r-hCG in OI (Study 8209)

Parameter	Ovidrel® 250 µg (n = 99)
Ovulation Rate	91 (91.9%)
Clinical Pregnancy Rate*	22 (22%)

* Clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heartbeat activity) was detected by ultrasound on day 35-42 after hCG administration.

For the 22 patients who had a clinical pregnancy with Ovidrel® 250 µg, the outcome of the pregnancy is presented in Table 8.

Table 8: Pregnancy Outcomes of r-hCG in OI (Study 8209)

Parameter	Ovidrel® 250 µg (n = 22)
Clinical Pregnancies not reaching term	7 (31.8%)
Live births	15 (68.2%)
Singleton	13 (86.7%)
Multiple birth	2 (13.3%)

INDICATIONS AND USAGE

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

Selection of Patients

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

CONTRAINDICATIONS

Ovidrel® PreFilled Syringe (choriogonadotropin alfa injection) is contraindicated in women who exhibit:

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

WARNINGS

Gonadotropins, including Ovidrel® PreFilled Syringe (choriogonado-tropin alfa injection), should only be used by physicians who are thoroughly familiar with infertility problems and their management. Like other hCG products, Ovidrel® PreFilled Syringe is a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) in women with or without pulmonary or vascular complications. The risks of gonadoptropin treatment should be considered for women with risk factors of thromboembolic events such as prior medical or family history. Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and requires the availability of appropriate monitoring facilities (see "**Precautions/ Laboratory Tests**"). Safe and effective induction of ovulation and use of Ovidrel® PreFilled Syringe in women requires monitoring of ovarian response with serum estradiol and transvaginal ultrasound on a regular basis.

Overstimulation of the Ovary Following hCG Therapy

Ovarian Enlargement

Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal

distention and/or abdominal pain may occur in patients treated with FSH and hCG, and generally regresses without treatment within two or three weeks. Careful monitoring of ovarian response can further minimize the risk of overstimulation.

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

Ovarian Hyperstimulation Syndrome (OHSS)

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

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

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

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

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

Multiple Births

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

Pulmonary and Vascular Complications

As with other hCG products, a potential for the occurrence of arterial thromboembolism exists.

PRECAUTIONS

General

Careful attention should be given to the diagnosis of infertility in candidates for hCG therapy. (see

"**Indications and Usage/ Selection of Patients**"). After the exclusion of pre-existing conditions, elevations in ALT were found in 10 (3%) of 335 patients receiving Ovidrel® 250 µg, 9 (10%) of 89 patients receiving Ovidrel® 500 µg and in 16 (4.8%) of 328 patients receiving urinary-derived hCG. The elevations ranged up to 1.2 times the upper limit of normal. The clinical significance of these findings is not known.

Information for Patients

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

Laboratory Tests

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

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

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy

Intrauterine death and impaired parturition were observed in pregnant rats given a dose of urinary-hCG

(500 IU) equivalent to three times the maximum human dose of 10,000 USP, based on body surface area.

Nursing Mothers

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

Pediatric Patients

Safety and effectiveness in pediatric patients has not been established.

Geriatric Patients

Safety and effectiveness in geriatric patients has not been established.

ADVERSE REACTIONS

(see **WARNINGS**)

The safety of Ovidrel® was examined in four clinical studies that treated 752 patients of whom 335 received Ovidrel® 250 µg following follicular recruitment with gonadotropins. When patients enrolled in four clinical studies (3 in ART and one in OI) were injected subcutaneously with either Ovidrel® or an approved urinary-derived hCG, 14.6 % (49 of 335 patients) in the Ovidrel® 250 µg group experienced application site disorders compared to 28% (92 of 328 patients) in the approved u-hCG group. Adverse events reported for Ovidrel® 250 µg occurring in at least 2% of patients (regardless of causality) are listed in Table 9 for the 3 ART studies and in Table 10 for the single OI study.

Table 9: Incidence of Adverse Events of r-hCG in ART (Studies 7648, 7927, 9073)

Body System	**Ovidrel® 250 µg (n=236)**
Preferred Term	**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)

Adverse events not listed in Table 9 that occurred in less than 2% of patients treated with Ovidrel® 250 µg whether or not considered causally related to Ovidrel®, included: injection site inflammation and reaction, flatulence, diarrhea, hiccup, ectopic pregnancy, breast pain, intermenstrual bleeding, vaginal hemorrhage, cervical lesion, leukorrhea, ovarian hyperstimulation, uterine disorders, vaginitis, vaginal discomfort, body pain, back pain, fever, dizziness, headache, hot flashes, malaise, paraesthesias, rash, emotional lability, insomnia, upper respiratory tract infection, cough, dysuria, urinary tract infection, urinary incontinence, albuminuria, cardiac arrhythmia, genital moniliasis, genital herpes, leukocytosis,

heart murmur and cervical carcinoma.

Table 10: Incidence of Adverse Events of r-hCG in Ovulation Induction (Study 8209)

Body System	**Ovidrel® 250 µg (n=99)**
Preferred Term	**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)

Additional adverse events not listed in Table 10 that occurred in less than 2% of patients treated with Ovidrel® 250 µg, whether or not considered causally related to Ovidrel®, included: breast pain, flatulence, abdominal enlargement, pharyngitis, upper respiratory tract infection, hyperglycemia and pruritis.

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

1. Spontaneous Abortion
2. Ectopic Pregnancy
3. Premature Labor
4. Postpartum Fever
5. Congenital Abnormalities

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

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

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

There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who

have undergone multiple drug regimens for ovulation induction; however, a causal relationship has not been established.

Post-Marketing Experience

In addition to adverse events reported from clinical trials, the following events have been reported during post-marketing use of Ovidrel®. Therefore, these events were reported from a population of uncertain size, the frequency or causal relationship to Ovidrel® cannot be reliably determined.

- Cases of allergic reactions, including anaphylactic reactions and mild reversible skin rashes have been reported in patients treated with Ovidrel® since market introduction. The causal relationship is unknown.
- Thromboembolic events both in association with, and separate from, the Ovarian Hyperstimulation Syndrome (see "WARNINGS")

DOSAGE AND ADMINISTRATION

For Subcutaneous Use Only

Infertile Women Undergoing Assisted Reproductive Technologies (ART)

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

Infertile Women Undergoing Ovulation Induction (OI)

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

Ovidrel® PreFilled Syringe 250 µg should be administered one day following the last dose of the follicle stimulating agent.

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

Directions for Administration of Ovidrel® Prefilled Syringe

Ovidrel® PreFilled Syringe is intended for a single subcutaneous injection. Any unused material should be discarded.

Ovidrel® PreFilled Syringe may be self-administered by the patient. Follow the directions below for injecting Ovidrel® PreFilled Syringe.

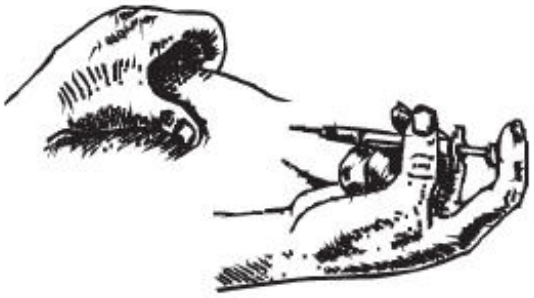
Step 1: Wash your hands thoroughly with soap and water.

Step 2: Carefully clean the injection site.

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

Step 3: Administer your injection.

Carefully remove the needle cap from the syringe. Do not touch the needle or allow the needle to touch any surface. Inject the prescribed dose as directed by your doctor, nurse or pharmacist.



Step 4: Gently withdraw the needle.

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

Step 5: Storage and clean up.

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

HOW SUPPLIED

Ovidrel® PreFilled Syringe (choriogonadotropin alfa injection) is supplied in a sterile, liquid single dose pre-filled 1 mL syringe. Each Ovidrel® PreFilled Syringe is filled with 0.515 mL containing 257.5 µg of choriogonadotropin alfa, 28.1 mg mannitol, 505 µg 85% O-phosphoric acid, 103 µg L-methionine, 51.5 µg Poloxamer 188, Sodium Hydroxide (for pH adjustment), and Water for Injection to deliver 250 µg of choriogonadotropin alfa in 0.5 mL.

The following package combination is available:

- 1 pre-filled syringe containing 250 µg Ovidrel® PreFilled Syringe NDC 44087-1150-1

Storage

The Ovidrel® PreFilled Syringe must be stored refrigerated between 2-8°C (36-46°F) before being dispensed to the patient. Patients should store the pre-filled syringe refrigerated to allow the product to be used until the expiry date shown on the syringe or carton. The Ovidrel® PreFilled Syringe may be stored by the patient for no more than 30 days at room temperature (up to 25°C (77°F) but must be used within those 30 days.

Protect from light.

Store in original package. Discard unused material.

Rx Only

Manufactured For:

EMD Serono, Inc. Rockland, MA 02370

June 2018

PRINCIPAL DISPLAY PANEL - 250 µg/0.5 mL Syringe Carton

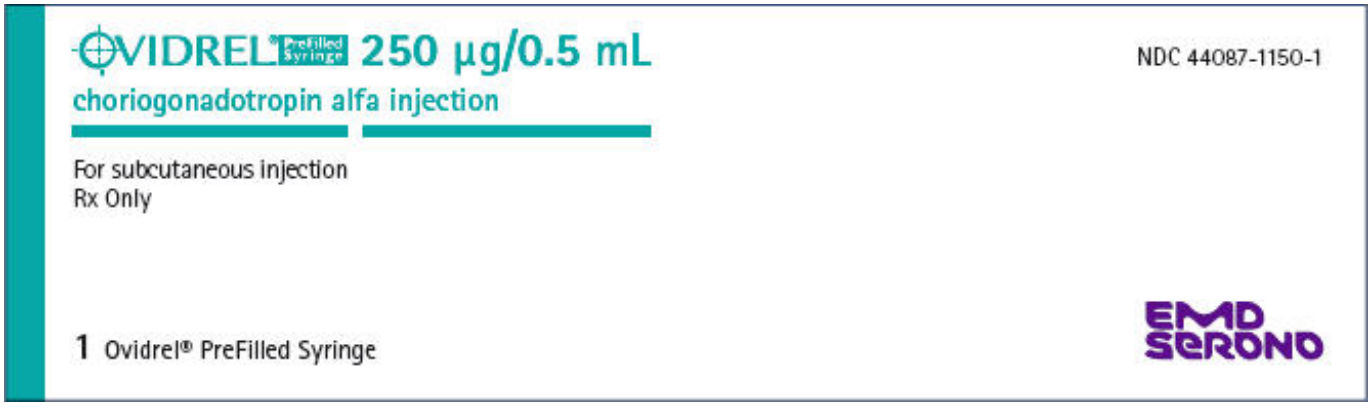
OVIDREL®
PreFilled
Syringe
250 µg/0.5 mL
choriogonadotropin alfa injection

NDC 44087-1150-1

For subcutaneous injection
Rx Only

1 Ovidrel® PreFilled Syringe

EMD
SERONO



OVIDREL

choriogonadotropin alfa injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:44087-1150
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CHORIOGONADOTROPIN ALFA (UNII: 6413W06WR3) (CHORIOGONADOTROPIN ALFA - UNII:6413W06WR3)	CHORIOGONADOTROPIN ALFA	250 ug in 0.5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
MANNITOL (UNII: 3OWL53L36A)	
PHOSPHORIC ACID (UNII: E4GA8884NN)	

METHIONINE (UNII: AE28F7PNPL)	
POLOXAMER 188 (UNII: LQA7B6G8JG)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:44087-1150-1	1 in 1 CARTON	10/06/2003	
1		0.5 mL in 1 SYRINGE, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021149	10/06/2003	

Labeler - EMD Serono, Inc. (088514898)

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