Ovidrel®

(choriogonadotropin alfa for injection)

FOR SUBCUTANEOUS USE

DESCRIPTION

Ovidrel® (choriogonadotropin alfa for injection) is a sterile lyophilized powder composed of choriogonadotropin alfa (recombinant human Chorionic Gonadotropin, r-hCG), sucrose and phosphoric acid. The drug substance is produced by recombinant DNA techniques. 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® is a sterile, lyophilized powder intended for subcutaneous (SC) injection after reconstitution with Sterile Water for Injection, USP. Each vial of Ovidrel® contains 285 mcg of choriogonadotropin alfa, 30 mg Sucrose, 0.98 mg Phosphoric acid, and Sodium Hydroxide (for pH adjustment) which, when reconstituted with the diluent, will deliver 250 mcg of recombinant human Chorionic Gonadotropin. The pH of reconstituted 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®, 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® 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 mcg to 1000 mcg. Pharmacokinetic parameter estimates following SC administration of Ovidrel® 250 mcg 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 mcg 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 mcg, 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 mcg 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 mcg 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 mcg 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.

Special populations: Safety, efficacy, and pharmacokinetics of Ovidrel® 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® 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 mcg and Ovidrel® 500 mcg 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 mcg. 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 mcg and Ovidrel®

500 mcg 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 mcg are summarized in Table 2.

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 (%)	35.1
Clinical pregnancy rate per transfer (%)	36.3

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)
*nmol/L ÷ 3.18 = ng/mL

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

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%)
Singleton	*20 (69.0%)*
Multiple birth	*9 (31.0%)*

The safety and efficacy of Ovidrel® 250 mcg 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 mcg. The efficacy of Ovidrel® 250 mcg 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 mcg are summarized in Table 4.

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 (%)	33
Clinical pregnancy rate per transfer (%)	37.6

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)

* nmol/L ÷ 3.18 = ng/mL

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

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

Parameter	**Ovidrel® 250 mcg**

	(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 mcg 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 mcg. The efficacy of Ovidrel® 250 mcg 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 mcg are summarized in Table 6.

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†	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 mcg, the outcome of the pregnancy is presented in Table 7.

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%)
Singleton	*13 (86.7%)*
Multiple birth	*2 (13.3%)*

INDICATIONS AND USAGE

Ovidrel® (choriogonadotropin alfa for 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® 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® 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® therapy.
5. Evaluation of the partner's fertility potential should be included in the initial evaluation.

CONTRAINDICATIONS

Ovidrel® (choriogonadotropin alfa for 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® (choriogonadotropin alfa for injection), should only be used by physicians who are thoroughly familiar with infertility problems and their management. Like other hCG products, Ovidrel® is a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) in women with or without pulmonary or vascular complications. 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® 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 mcg 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 mcg. Two patients treated with Ovidrel® 500 mcg 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 mcg 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 mcg, 9 (10%) of 89 patients receiving Ovidrel® 500 mcg 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: Pregnancy Category X. Fetal death and impaired parturition were observed in pregnant rats given a dose of choriogonadotropin alfa (25 mcg/day) equivalent to six times the maximum human dose of 250 mcg 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 mcg 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® 250mcg group experienced application site disorders compared to 28% (92 of 328 patients) in the approved u-hCG group. Adverse events reported for Ovidrel® 250 mcg occurring in at least 2% of patients (regardless of causality) are listed in Table 8 for the 3 ART studies and in Table 9 for the single OI study.

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)

Adverse events not listed in Table 8 that occurred in less than 2% of patients treated with Ovidrel® 250 mcg 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 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)

Additional adverse events not listed in Table 9 that occurred in less than 2% of patients treated with Ovidrel® 250 mcg, 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 mcg or 500 mcg, three were associated with a congenital anomaly of the fetus or newborn. Among patients receiving Ovidrel® 250 mcg, 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 mcg, 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.

DOSAGE AND ADMINISTRATION

For Subcutaneous Use Only

Infertile Women Undergoing Assisted Reproductive Technologies (ART)

Ovidrel® 250 mcg should be administered one day following the last dose of the follicle stimulating agent. Ovidrel® 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® should not be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography.

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

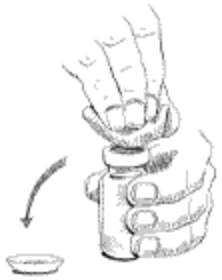
Ovidrel® administration should be withheld in situations where there is an excessive ovarian response, as evidenced by multiple follicular development, clinically significant ovarian enlargement or excessive estradiol production.

Directions for Administration of Ovidrel®:

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

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

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

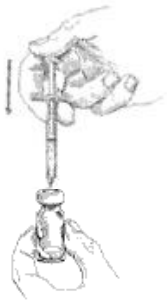


After removing the plastic flip-tops with your thumb, wipe the rubber stoppers with alcohol. The rubber stoppers should not be touched after they are wiped.

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

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

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



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

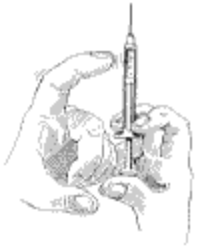
Step 4: Leaving the needle in the vial, gently rotate the vial. Do not shake.

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

Step 5: Withdraw the liquid from the vial.

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

Step 6: Remove any bubbles in the syringe.



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

Step 7: Recap the syringe needle.

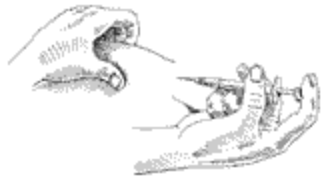
Recap the syringe needle. Do not touch the needle or allow the needle to touch any surface. Carefully lay the syringe down on a flat, clean surface.

Step 8: 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 9: Administer your injection.

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



Step 10: 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 11: Storage and clean up.

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

HOW SUPPLIED

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

The following package combinations is available:

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

NDC 44087-0250-1

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

Protect from light.

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

Rx Only

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