

PACKAGE INSERT

 **PREGNYL[®]**

(chorionic gonadotropin for injection, USP)

10,000 units/vial

Human Gonadotropin

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THERAPEUTIC CLASSIFICATION

Human Gonadotropin

ACTION

The action of human chorionic gonadotropin (hCG) is virtually identical to that of pituitary LH, although hCG appears to have a small degree of FSH activity as well. It stimulates production of gonadal steroid hormones by stimulating the interstitial cells (Leydig cells) of the testis to produce androgens and the corpus luteum of the ovary to produce progesterone.

Androgen stimulation in the male leads to the development of secondary sex characteristics and may stimulate testicular descent when no anatomical impediment to descent is present.

HCG has no known effect on fat mobilization, appetite or sense of hunger, or body fat distribution. Following IM administration, an increase in serum chorionic gonadotropin concentrations may be observed within 2 hours. Peak concentrations occur within 6 hours and persist for approximately 36 hours. Serum chorionic gonadotropin levels begin to decline at 48 hours reaching undetectable levels after 72 hours. Chorionic gonadotropin is distributed primarily in the testes and ovaries of the male and female respectively, with small amounts possible distributing into the proximal tubules of the renal cortex.

Blood levels of chorionic gonadotropin decline in a biphasic manner. The initial phase half-life has been reported between 5.6 and 11 hours, whereas the terminal phase half-life has been

reported between 23 and 37.2 hours. Following IM administration of therapeutic doses, approximately 10-12% of the dose is excreted in urine within 24 hours.

INDICATION

Pregnyl[®] (chorionic gonadotropin for injection, USP) is indicated for:

- 1) Prepubertal cryptorchidism not due to anatomical obstruction. In general, hCG is thought to induce testicular descent in situations when descent would have occurred at puberty. HCG thus may help predict whether or not orchiopexy will be needed in the future.
- 2) Selected cases of hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males.
- 3) Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure, and who has been appropriately pretreated with FSH-containing preparations.

NOTE: hCG has not been demonstrated to be effective adjunctive therapy in the treatment of obesity. There is no substantial evidence that it increases weight loss beyond that resulting from caloric restriction, that it causes a more attractive or “normal” distribution of fat, or that it decreases the hunger and discomfort associated with calorie-restricted diets.

CONTRAINDICATIONS

Pregnyl[®] (chorionic gonadotropin for injection, USP) is contraindicated for Prepubertal boys with signs of anatomical obstruction and for patients with:

- Precocious puberty

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container (see WARNINGS AND PRECAUTIONS).
- Known or suspected sex hormone-dependent tumours, such as ovary, breast and uterine carcinoma in female and prostatic or breast carcinoma in the male.
- Malformations of the reproductive organs incompatible with pregnancy.
- Fibroid tumours of the uterus incompatible with pregnancy.
- Abnormal (not menstrual) vaginal bleeding without a known/diagnosed cause.

WARNINGS AND PRECAUTIONS

HCG should be used in conjunction with FSH-containing preparations only by physicians experienced with infertility problems who are familiar with the criteria for patient selection, contraindications, warnings and precautions, and adverse reactions described in the package insert for FSH-containing preparations.

The drug substance of this product is manufactured from human urine. Although the risk is theoretical, and no case of transmission of an infectious agent linked to the use of urine-derived gonadotropins has ever been identified, the risk of transmitting infectious agents cannot be completely excluded.

Anaphylaxis and other hypersensitivity reactions have been reported with urinary derived HCG products.

For males and females:

Hypersensitivity reactions:

- **Hypersensitivity reactions, both generalized and local; anaphylaxis; and angioedema have been reported. If a hypersensitivity reaction is suspected,**

discontinue Pregnyl and assess for other potential causes for the event. (See CONTRAINDICATIONS.)

General:

- Patients should be evaluated for uncontrolled non-gonadal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders) and appropriate specific treatment given.
- Pregnyl should not be used for body weight reduction. HCG has no effect on fat metabolism, fat distribution or appetite.

In the female:

Multi-fetal gestation and birth:

- In pregnancies occurring after induction of ovulation with gonadotropic preparations, there is an increased risk of multiple pregnancies.

Ectopic pregnancy:

- Infertile women undergoing Assisted Reproductive Technologies (ART) have an increased incidence of ectopic pregnancy. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.

Pregnancy loss:

- Rates of pregnancy loss in women undergoing assisted reproductive technologies (ART) are higher than in the normal population.

Congenital Malformations:

- The incidence of congenital malformations after assisted reproductive technologies may be slightly higher than after spontaneous conceptions. This slightly higher incidence is thought to be related to differences in parental characteristics (e.g.,

maternal age, sperm characteristics) and to the higher incidence of multiple gestations after assisted reproductive technologies. There are no indications that the use of gonadotropins during assisted reproductive technologies is associated with an increased risk of congenital malformations.

Ovarian Hyperstimulation Syndrome (OHSS):

- OHSS is a medical event distinct from uncomplicated ovarian enlargement. Clinical signs and symptoms of mild and moderate OHSS are abdominal pain, nausea, diarrhea, mild to moderate enlargement of ovaries and ovarian cysts. Severe OHSS may be life-threatening. Clinical signs and symptoms of severe OHSS are large ovarian cysts, acute abdominal pain, ascites, pleural effusion, hydrothorax, dyspnea, oliguria, hematological abnormalities and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS. Transient liver function test abnormalities suggestive of hepatic dysfunction with or without morphologic changes on liver biopsy have also been reported in association with OHSS.

OHSS may be caused by administration of human Chorionic Gonadotropin (hCG) and by pregnancy (endogenous hCG). Early OHSS usually occurs within 10 days after hCG administration and may be associated with an excessive ovarian response to gonadotropin stimulation. Late OHSS occurs more than 10 days after hCG administration, as a consequence of the hormonal changes with pregnancy. Because of the risk of developing OHSS, patients should be monitored for at least two weeks after hCG administration.

Women with known risk factors for a high ovarian response may be especially prone to the development of OHSS during or following treatment with Pregnyl. For women having their first cycle of ovarian stimulation, for whom risk factors are

only partially known, close observation for early signs and symptoms of OHSS is recommended.

To reduce the risk of OHSS, ultrasonographic assessments of follicular development should be performed prior to treatment and at regular intervals during treatment. The concurrent determination of serum estradiol levels may also be useful. In ART, there is an increased risk of OHSS with 18 or more follicles of 11 mm or more in diameter. When there are 30 or more follicles in total, it is advised to withhold hCG administration.

Depending on the ovarian response, the following measures can be considered to reduce the risk of OHSS:

- withhold further stimulation with a gonadotropin for a maximum of 3 days (coasting);
- withhold hCG and cancel the treatment cycle;
- administer a dose lower than 10,000 IU of urinary hCG for triggering final oocyte maturation, e.g. 5,000 IU urinary hCG or 250 micrograms rec-hCG (which is equivalent to approximately 6,500 IU of urinary hCG);
- cancel the fresh embryo transfer and cryopreserve embryos;
- avoid administration of hCG for luteal phase support.

Adherence to the recommended Pregnyl dose and treatment regimen and careful monitoring of ovarian response is important to reduce the risk of OHSS. If OHSS develops, standard and appropriate management of OHSS should be implemented and followed.

Ovarian torsion:

- Ovarian torsion has been reported after treatment with gonadotropins, including Pregnyl. Ovarian torsion may be related to other conditions, such as OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, and previous or current ovarian cysts. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion.

Vascular Complications:

Thromboembolic events, both in association with and separate from OHSS, have been reported following treatment with gonadotropins, including Pregnyl. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital organs or the extremities. Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity or thrombophilia, may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotropins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.

In the male:

Antibody formation:

- Administration of hCG can provoke the formation of antibodies against hCG. In rare cases, this may result in an ineffective treatment.

Treatment with hCG leads to increased androgen production. Therefore:

- Patients with latent or overt cardiac failure, renal dysfunction, hypertension, epilepsy, migraine or asthma (or a history of these conditions) should be kept under

close medical supervision, since aggravation or recurrence may occasionally be induced as a result of increased androgen production.

- hCG should be used cautiously in prepubertal boys to avoid premature epiphyseal closure or precocious sexual development. Skeletal maturation should be monitored regularly.

Neurologic

As far as known this medicine has no influence on alertness and concentration.

Special populations

Pregnant women:

Pregnyl[®] should not be used after pregnancy is established.

Nursing women:

Pregnyl[®] must not be used during lactation.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Headache, irritability, restlessness, depression, fatigue, edema, precocious puberty, gynecomastia as well as pain at the injection site have been reported during treatment with Pregnyl[®] (chorionic gonadotropin for injection, USP). Ovarian cancer has also been reported in a very small number of infertile women who have been treated with fertility drugs. A causal relationship between treatment with fertility drugs and ovarian cancer has not been established.

Clinical Trial Adverse Drug Reactions

Clinical trials are conducted under very specific conditions and therefore, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another member of the therapeutic class. Frequencies of adverse drug reactions from clinical trials with Pregnyl[®] is not available because that information was not being collected by the system used in current drug development.

Post-Market Adverse Drug Reactions

General Disorders and Administrative Site Conditions

Pregnyl[®] may cause reactions at the site of injection, such as bruising, pain, redness, swelling and itching. Occasionally allergic reactions have been reported, mostly manifesting as pain and/or rash at the injection site. Weight gain has been observed as part of the clinical picture of severe OHSS.

Immune System Disorders

In rare cases generalized rash or fever may occur.

In the Female:

Gastrointestinal Disorders

Abdominal pain and gastrointestinal symptoms such as nausea and diarrhea, related to mild OHSS. Ascites, as a complication of severe OHSS.

Reproductive and Breast Disorders

Unwanted ovarian hyperstimulation, mild or severe OHSS (see WARNINGS AND PRECAUTIONS).

Painful breasts, mild to moderate enlargement of ovaries and ovarian cysts related to mild OHSS.
Large ovarian cysts (prone to rupture), usually associated with severe OHSS.

Respiratory, Thoracic and Mediastinal Disorders

Hydrothorax, as a complication of severe OHSS.

Vascular Disorders

In rare instances, thromboembolism has been associated with FSH/hCG therapy, usually associated with severe OHSS (see WARNINGS AND PRECAUTIONS).

In the Male:

Metabolism and Nutrition Disorders

Water and sodium retention is occasionally seen after administration of high dosages; this is regarded as a result of excessive androgen production.

Reproductive System and Breast Disorders

HCG treatment may sporadically cause gynecomastia.

DRUG INTERACTIONS

Interactions of Pregnyl[®] (chorionic gonadotropin for injection, USP) with other medicines have not been investigated; interactions with commonly used medicinal products can therefore not be excluded.

Following administration, Pregnyl[®] may interfere for up to ten days with the immunological determination of serum/urinary hCG, leading to a false positive pregnancy test.

DOSAGE AND ADMINISTRATION

FOR INTRAMUSCULAR USE ONLY after reconstitution of the dry powder with the sterile diluent. Although the dosage regimen will depend upon the indication, the patient's age and weight, and the prescriber's preference, the following regimens have been advocated by various authorities.

Males:

Prepubertal cryptorchidism not due to anatomical obstruction

4,000 USP units, 3 times weekly, for 2 to 3 weeks, or 1,000 USP units, 3 times weekly for 6 to 8 weeks. The dosage schedule may vary to some extent, depending upon the age when treatment is given. If the dosage is adequate, there will usually be some indication, following one such course of therapy, whether descent will occur or surgery be required.

A therapeutic trial with chorionic gonadotropin may constitute a valuable diagnostic aid to determine the need for surgery. Lack of response is usually an indication of anatomic obstruction. Furthermore, when surgery is required, the preliminary treatment may facilitate the procedure by increasing the size of the testes and the length of the cords. Postoperative gonadotropic therapy has also been suggested to prevent retraction of testes.

Age of initiation of treatment: Various ages ranging from early childhood to immediately before expected puberty have been suggested. The average appropriate age, however, appears to be 12 years.

Selected cases of hypogonadotropic hypogonadism in males

4,000 to 5,000 USP units 3 times weekly for 6 to 8 weeks with a rest of period of 2 to 3 weeks between courses of therapy.

Females:

Induction of ovulation and pregnancy in the anovulatory infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure and who has been appropriately pretreated with FSH-containing preparations (see prescribing information of FSH-containing preparations for dosage and administration for those drug products).

5,000 to 10,000 USP units one day following the last day of treatment with an FSH-containing preparation (a dosage of 10,000 USP units is recommended in the labeling of FSH-containing preparations).

PHARMACEUTICAL INFORMATION

Drug Substance:

Chorionic Gonadotropin

Description

Chorionic gonadotropin is a glycoprotein substance, with a molecular weight of approximately 38600 secreted by the placenta and obtained from the urine of pregnant women. It is composed of nonidentical and noncovalently linked α and β subunits. The α subunits of CG is essentially identical to the α subunits of the human pituitary gonadotropins, luteinizing hormone and follicle stimulation hormone, as well as to the α subunit of human TSH, however the β subunit of CG differs in amino acid sequence from the other hormones.

Chorionic gonadotropin occurs as a white or practically white, amorphous powder and is freely soluble in water.

Composition:

Each vial of Pregnyl[®] (chorionic gonadotropin for injection, USP) contains: 10,000 USP units of sterile lyophilized human chorionic gonadotropin plus 5 mg of monobasic sodium phosphate monohydrate and 4.4 mg of dibasic sodium phosphate anhydrous (pH may have been adjusted

with sodium hydroxide and/or phosphoric acid).

Each vial of Pregnyl[®] solvent contains: 10mL of Water for Injection, 0.9% of benzyl alcohol, 0.56% sodium chloride and trace amount of sodium hydroxide and/or hydrochloric acid.

Stability and Storage Recommendations:

Store at 15°C - 30°C.

Reconstituted solution is stable for 28 days when refrigerated (2°C - 8°C).

Incompatibilities:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Reconstituted Solution:

Direction for reconstitution

Reconstitute Pregnyl[®] 10,000 USP units to the desired concentration by addition of the required amount of the solvent supplied. Remove 1 to 10 mL of the solvent and add to the vial with the lyophilized Pregnyl[®], agitate gently until the powder is completely dissolved.

When reconstituted with 10mL of the solvent, the concentration of Chorionic Gonadotropin is 1,000 USP units/mL. The solvent contains 0.9% benzyl alcohol.

AVAILABILITY

Each package contains two vials: one multi-dose vial of Pregnyl[®] (chorionic gonadotropin for injection, USP) 10,000 USP units plus one vial of 10 mL sterile Pregnyl[®] solvent.

Please note that Pregnyl[®] does not fall under the scope of the “New Drugs” regulation.

Therefore, some of the headings in the new Product Monograph format are not applicable.