

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. This descent may be reversible, on extremely rare occasions, when hCG is discontinued.

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. Descent following hCG administration is usually permanent.
- 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.
- 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 sexual organs incompatible with pregnancy.
- Fibroid tumours of the uterus incompatible with pregnancy.

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.

IN THE FEMALE:

IN PREGNANCIES OCCURRING AFTER INDUCTION OF OVULATION WITH GONADOTROPIC PREPARATIONS, THERE IS AN INCREASED RISK OF MULTIPLETS.

SINCE INFERTILE WOMEN UNDERGOING ASSISTED REPRODUCTION, AND PARTICULARLY IVF, OFTEN HAVE TUBAL ABNORMALITIES THE INCIDENCE OF ECTOPIC PREGNANCIES MIGHT BE INCREASED. EARLY ULTRASOUND CONFIRMATION THAT A PREGNANCY IS INTRAUTERINE IS THEREFORE IMPORTANT.

RATES OF PREGNANCY LOSS IN WOMEN UNDERGOING ASSISTED REPRODUCTIVE TECHNOLOGIES (ART) ARE HIGHER THAN IN THE NORMAL POPULATION.

THE PRESENCE OF UNCONTROLLED NON-GONADAL ENDOCRINOPATHIES (E.G. THYROID, ADRENAL OR PITUITARY DISORDERS) SHOULD BE RULED OUT.

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.

UNWANTED OVARIAN HYPERSTIMULATION

IN PATIENTS TREATED FOR SUBFERTILITY DUE TO ANOVULATION OR IMPAIRED FOLLICULAR RIPENING, THE PRIOR ADMINISTRATION OF AN FSH-CONTAINING PREPARATION MAY LEAD TO UNWANTED OVARIAN HYPERSTIMULATION. THEREFORE ULTRASONIC ASSESSMENT OF FOLLICULAR DEVELOPMENT AND DETERMINATIONS OF ESTRADIOL LEVELS SHOULD BE PERFORMED PRIOR TO FSH-TREATMENT AND AT REGULAR INTERVALS DURING FSH-TREATMENT. ESTRADIOL LEVELS MAY RISE VERY RAPIDLY, E.G. MORE THAN A DAILY DOUBLING FOR TWO OR THREE CONSECUTIVE DAYS, AND POSSIBLY REACH EXCESSIVELY HIGH VALUES. THE DIAGNOSIS OF UNWANTED OVARIAN HYPERSTIMULATION MAY BE CONFIRMED BY ULTRASOUND EXAMINATION. IF THIS UNWANTED OVARIAN HYPERSTIMULATION OCCURS (I.E. NOT AS PART OF A TREATMENT PREPARING FOR IVF/ET, GIFT OR ICSI), THE ADMINISTRATION OF THE FSH-CONTAINING PREPARATION SHOULD BE DISCONTINUED IMMEDIATELY. IN THAT CASE PREGNANCY SHOULD BE AVOIDED AND PREGNYL® (CHORIONIC GONADOTROPIN FOR INJECTION, USP) MUST NOT BE GIVEN, BECAUSE THE ADMINISTRATION OF AN LH-ACTIVE GONADOTROPIN AT THIS STAGE MAY INDUCE, IN ADDITION TO MULTIPLE OVULATIONS, THE OVARIAN HYPERSTIMULATION SYNDROME (OHSS). THIS WARNING IS PARTICULARLY IMPORTANT WITH RESPECT TO PATIENTS WITH POLYCYSTIC OVARIAN DISEASE. CLINICAL SYMPTOMS OF MILD OVARIAN HYPERSTIMULATION SYNDROME ARE GASTRO-INTESTINAL PROBLEMS (PAIN, NAUSEA, DIARRHEA), PAINFUL BREASTS, AND MILD TO MODERATE

ENLARGEMENT OF OVARIES AND OVARIAN CYSTS. 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. IN RARE CASES SEVERE OVARIAN HYPERSTIMULATION SYNDROME OCCURS, WHICH MAY BE LIFE-THREATENING. THIS IS CHARACTERIZED BY LARGE OVARIAN CYSTS (PRONE TO RUPTURE), ASCITES, WEIGHT GAIN, OFTEN HYDROTHORAX AND OCCASIONALLY THROMBOEMBOLIC PHENOMENA.

WOMEN WITH GENERALLY RECOGNISED RISK FACTORS FOR THROMBOSIS, SUCH AS A PERSONAL OR FAMILY HISTORY, SEVERE OBESITY (BODY MASS INDEX > 30 KG/M²) 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.

PREGNYL[®] SHOULD NOT BE USED FOR BODY WEIGHT REDUCTION. HCG HAS NO EFFECT ON FAT METABOLISM, FAT DISTRIBUTION OR APPETITE.

IN THE MALE:

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.

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.

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.

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.