

PRESCRIBING INFORMATION

PrChorionic Gonadotropin for Injection, USP

10 000 USP Units

Sterile Lyophilized Powder

For Intramuscular or Subcutaneous Use

Gonadotropin

Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON M9W 0C8

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DESCRIPTION

Chorionic Gonadotropin for Injection, USP (hCG) is extracted from the urine of pregnant women. It is a water-soluble polypeptide hormone produced by the human placenta composed of an alpha and a beta sub-unit. The alpha sub-unit is essentially identical to the alpha sub-units of the human pituitary gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), as well as to the alpha sub-unit of human thyroid-stimulating hormone (TSH). The beta sub-units of these hormones differ in amino acid sequence.

Chorionic Gonadotropin for Injection, USP (hCG) is biologically standardized and the potency is declared in terms of the USP Reference Standard.

ACTIONS

The action of hCG is virtually identical to that of pituitary LH, although hCG appears to have a small degree of FSH activity as well.

Male: Chorionic Gonadotropin for Injection, USP is given to males in an effort to stimulate the interstitial cells of the testes (cells of Leydig) to produce androgen. The response to hCG may be considered similar to the effect caused by the interstitial cell stimulating hormone (ICSH) from the anterior lobe of the pituitary. 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 is usually reversible when hCG is discontinued.

Chorionic Gonadotropin for Injection, USP is likely to be of benefit in all conditions directly related to insufficient secretion of androgen, provided the interstitial cells of the testes are capable of stimulation.

Female: Chorionic Gonadotropin for Injection, USP is given in the second phase of the cycle in an effort to maintain the functional integrity of the corpus luteum and to stimulate its secretion of progesterone. Response to hCG may be considered similar to the effect caused by the luteotrophic hormone from the pituitary gland.

During the normal menstrual cycle, LH participates with FSH in the development and maturation of the normal ovarian follicle, and the mid-cycle LH surge triggers ovulation. HCG can substitute for LH in this function.

During a normal pregnancy, hCG secreted by the placenta maintains the corpus luteum after LH secretion decreases, supporting continued secretion of estrogen and progesterone and preventing menstruation.

HCG has no known effect on fat mobilization, appetite or sense of hunger, or body fat distribution.

INDICATIONS AND CLINICAL USE

Note: hCG has not been shown to be an 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 produces a more attractive or "normal" distribution of fat, or that it reduces the hunger and discomfort associated with calorie-restricted diets.

Male:

Chorionic Gonadotropin for Injection, USP is indicated for the treatment of:

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. Thus, hCG may help predict whether or not orchiopexy will be needed in the future. In most cases the response is temporary, although, in some cases, descent after hCG administration is permanent. Age of initiation of treatment: various ages ranging from early childhood to immediately before expected puberty have been suggested. On the average, however, 12 years appears to be the appropriate age.

2. Delayed Adolescence

Chorionic gonadotropin will almost invariably set in motion the normal mechanism of puberty by stimulating the interstitial cells to secrete androgen. Normal development is likely to continue after therapy ceases.

3. Dwarfism (pituitary)

Before epiphyseal closure, the stimulative effects of chorionic gonadotropin on the interstitial cells of the testes may prove beneficial. Therapy has produced acceleration of longitudinal bone growth as well as sexual and somatic maturation in some cases.

4. Hypogonadotropic Eunuchoidism

Chorionic gonadotropin therapy is directed to the development of primary and secondary sex characteristics through its ability to stimulate the interstitial cells of the testes to secrete androgen. The response to hCG is usually dramatic in patients of pubertal age. The adult patient does not respond as readily, but in light of the permanent effects frequently observed after hCG therapy, it is recommended that in either group, treatment be initiated with this substance, and that androgen be used only if hCG proves ineffective.

5. Selected Cases of Hypogonadotropic Hypogonadism (hypogonadism secondary to a pituitary deficiency) in Males

On clinical grounds alone, it is often impossible to determine whether the hypogonadism is the result of primary testicular failure. When testicular biopsies and urinary gonadotropin assays are not available, a therapeutic trial with hCG will assist in establishing a diagnosis and indicate the type of treatment required.

Lack of response to Chorionic Gonadotropin for Injection, USP therapy may be considered as an indication that the hypogonadism is not of pituitary origin, or that the testes are unresponsive to stimulation. If this is the case, substitution therapy with androgen is indicated.

Female:

Chorionic Gonadotropin for Injection, USP is indicated for:

1. Ovulation Induction

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 pre-treated with human gonadotropins.

2. Abortion (habitual)

Recurrent abortion at the end of the first three to six weeks of pregnancy may be due to inadequate production of chorionic gonadotropin. The administration of large daily doses of Chorionic Gonadotropin for Injection, USP may provide a beneficial luteotropic effect in the habitual aborter. Preconceptional treatment with hCG may encourage nidation and promote a more favourable environment for implantation and early development of the ovum.

3. Infrequent Scanty Bleeding (functional)

Oligomenorrhea, amenorrhea (primary and secondary), and Frohlich's Syndrome.

4. Functional Sterility

Functional sterility may not be due to ovulatory failure but to corpus luteum development and function which is inadequate for proper implantation and early development of the fertilized ovum. In such instances, chorionic gonadotropin may be used in an effort to stimulate progesterone secretion and to encourage a return to normal ovarian function.

CONTRAINDICATIONS

Chorionic Gonadotropin for Injection, USP is contraindicated in the treatment of:

- pituitary tumour, ovarian tumour, prostatic carcinoma and androgen-dependent neoplasms, uncontrolled endocrine disorders (e.g., hyperprolactinemia, thyroid and adrenal dysfunction);
- in female, primary ovarian failure (ovarian dysgenesis and premature menopause), tubal occlusion unless the patient is undergoing superovulation for *in vitro* fertilization;

- urinary-hCG (u-hCG) will not be effective in men, in cases where the FSH level is raised as this is indicative of primary testicular failure;
- u-hCG is not effective and is not indicated for weight reduction;
- precocious puberty;
- active thrombophlebitis or thromboembolic event;
- allergy to u-hCG;
- malformations of sexual organs incompatible with pregnancy;
- fibroid tumours of the uterus incompatible with pregnancy;
- prepubertal boys with signs of anatomical obstruction;
- known or suspected sex hormone-dependent tumors, such as ovary, breast and uterine carcinoma in female and prostatic or breast carcinoma in the male.

WARNINGS AND PRECAUTIONS

Chorionic Gonadotropin for Injection, USP 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 drug 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.

In the Female

- **Ovarian hyperstimulation syndrome (OHSS)**

An excessive ovarian response to follicular stimulating agents in women undergoing ovulation induction may lead to the development of ovarian hyperstimulation syndrome if u-hCG is given to induce ovulation or to support the corpus luteum. It is of utmost importance that u-hCG should be withheld in such cycles.

OHSS is generally categorized as mild, moderate or severe.

Mild OHSS symptoms: some abdominal distension; nausea; vomiting; occasional diarrhea; ovaries enlarged to about 5 cm diameter appear 3 – 6 days after u-hCG administration. Therapy: rest; careful observation and symptomatic relief. Enlargement of the ovaries decreases quickly.

Moderate OHSS symptoms: more pronounced abdominal distension; nausea; vomiting; occasional diarrhea; ovaries enlarge to about 12 cm. Therapy: bed rest; close observation in the case of conception occurring to detect any progression to severe hyperstimulation. In

order to avoid rupture of ovarian cysts, pelvic examination of enlarged ovaries should be gentle. Symptoms subside spontaneously over 2 – 3 weeks.

Severe OHSS is a rare (less than 2% of cases when patients are normally monitored) but serious complication. Symptoms: ovaries enlarge to in excess of 12 cm diameter; pronounced abdominal distension; ascites; pleural effusion; decreased blood volume; reduced urine output; electrolyte imbalance and sometimes shock. Diuretics should not be used in the primary phase of the syndrome, since they may precipitate cardiovascular shock in a patient who already has plasma hypovolemia. However, diuretics may be used during the resolution phase of OHSS to help mobilize and eliminate fluid sequestered during the first phase. Therapy: hospitalization, treatment should be conservative and concentrate on restoring fluid depletion and preventing shock. Acute symptoms subside over several days if conception has not occurred. Symptoms may persist longer if conception has occurred. The risk of OHSS developing in women undergoing superovulation for an assisted conception technique may be lessened if all the follicles are aspirated prior to ovulation.

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 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.

- **Rupture of ovarian cysts** with resultant hemoperitoneum.
- **Thromboembolic complications:** Thromboembolic events have been reported after gonadotropin/u-hCG therapy both in association with and separated from OHSS. These included thrombophlebitis, pulmonary embolism, stroke, and arterial occlusion resulting in loss of a limb. In rare instances, thromboembolic events have resulted in death. 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.

- **Multiple pregnancy:** The incidence of multiple pregnancies and births increases after gonadotropins/u-hCG therapy stimulation and ovulation induction in patients attempting *in vivo* conception. The risk of multiple pregnancy following ART is related to the number of oocytes/embryos replaced. However, the majority of multiple pregnancies are twins. Multiple pregnancies might result in premature deliveries.
- **Pregnancy testing:** A false positive test result may be obtained if the patient has recently undergone (over the last 7 days) u-hCG administration or is still receiving the drug.

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.

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 gonadotrophins during assisted reproductive technologies is associated with an increased risk of congenital malformations.

Chorionic Gonadotropin for Injection, USP should not be used for body weight reduction. HCG has no effect on fat metabolism, fat distribution or appetite.

In the male

- **Fluid retention:** If high doses of u-hCG are administered in males, the androgens may cause fluid retention. In such instances, the dose should be reduced considerably, particularly in patients with latent or overt cardiac or renal disease, hypertension, epilepsy, migraine or asthma (or a history of these conditions). Patients should be kept under close medical supervision, since aggravation or recurrence may occasionally be induced as a result of increased androgen production.
- **Sexual precocity:** u-hCG may cause sexual precocity when given to young patients for cryptorchidism. If signs are observed, cease treatment. If continued therapy is considered necessary, a reduced dosage regimen should be used.

- **Gynecomastia:** Gynecomastia may be induced by u-hCG.

Neurologic

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

Special populations

Pregnant women: Chorionic Gonadotropin for Injection, USP should not be used after pregnancy is established.

Nursing women: Chorionic Gonadotropin for Injection, USP must not be used during lactation.

Chorionic Gonadotropin for Injection, USP should not be used for body weight reduction. It has no effect on fat metabolism, fat distribution or appetite.

DRUG INTERACTIONS

No clinically significant drug interactions have been reported during u-hCG therapy.

Interactions of chorionic gonadotropin with other medicines have not been investigated; interactions with commonly used medicinal products can therefore not be excluded.

Chorionic gonadotropin may interfere with radioimmunoassay for gonadotropin, particularly luteinizing hormone.

Following administration, Chorionic Gonadotropin for Injection, USP may interfere for up to ten days with the immunological determination of serum/urinary hCG, leading to a false positive pregnancy test.

ADVERSE REACTIONS

The following adverse reactions have been associated with the administration of Chorionic Gonadotropin for Injection, USP: headache, irritability, restlessness, depression, fatigue, edema, precocious puberty, gynecomastia, pain at the site of injection.

Ovarian cancer has been reported in a very small number of infertile women who have been treated with fertility drugs. A causal relationship has not been established between treatment with fertility drugs and ovarian cancer.

Post-Market Adverse Drug Reactions

General Disorders and Administrative Site Conditions

Chorionic gonadotropin 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.

DOSAGE AND ADMINISTRATION

Dosage

The dosage regimen used in any particular case depends upon the indication for use, the age and weight of the patient, and the physician's preference.

Male

1. Prepubertal Cryptorchidism (not due to anatomical obstruction)

- a) 4000 USP units, three times weekly, for two to three weeks; or
- b) 1000 USP units, three times weekly, for six to eight weeks.

The dosage schedule may vary to some extent depending upon the age when treatment is given. If the dose 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 for Injection, USP 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, this 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 the testes.

2. Delayed Adolescence

4000 to 5000 USP units three times weekly for six to eight weeks with a rest period of two to three weeks between courses of therapy.

3. Dwarfism (pituitary)

1000 to 5000 USP units three times weekly.

4. Hypogonadotropic Eunuchoidism

4000 to 5000 USP units three times weekly for six to eight weeks with a rest period of two to three weeks between courses of therapy.

5. Hypogonadism (after sexual maturity)

4000 to 5000 USP units three times weekly for six to eight weeks with a rest period of two to three weeks between courses of therapy.

Female

1. Ovulation Induction

(For the gonadotropins dosage, see the prescribing information for that drug product.)
5000 to 10 000 USP units one day following the last dose of gonadotropins.

2. Abortion (habitual)

1000 to 2000 USP units, or more, one or more times daily combined with other recognized therapeutic measures until the danger of abortion has passed.

3. Infrequent Scanty Bleeding (functional)

Oligomenorrhea, amenorrhea (primary and secondary), and Frohlich's Syndrome: see dosage for **Functional Sterility**.

4. Functional Sterility

500 to 1000 USP units chorionic gonadotropin may be given daily from the 15th to the 24th day. An alternative schedule is 1500 USP units every other day, three times in all, on the 16th, 18th, and 20th day of the cycle.

Administration

Chorionic Gonadotropin for Injection, USP is **for subcutaneous or intramuscular use only**.

Preparation of Solution: Using a syringe, withdraw the sterile air from the vial containing the lyophilized chorionic gonadotropin and inject it into the diluent vial. Remove up to 10 mL from the diluent vial (see table below) and add to the Chorionic Gonadotropin for Injection, USP vial; mix gently until reconstitution is complete.

Parenteral drug products should be inspected visually prior to administration. Do not inject if the reconstituted product contains particulate matter or is discoloured.

Chorionic Gonadotropin for Injection, USP may be reconstituted by adding the required amount of diluent to obtain the desired dosage.

Table of Reconstitution and Administration Volumes

Desired Dosage (units)	Diluent Volume Options (mL)	Injection Volume (mL)
10 000	10	10
	5	5
	2.5	2.5
	1	1
5000	10	5
	5	2.5
	2.5	1.25
4000	10	4
	5	2
	2.5	1
2000	10	2
	5	1
	2.5	0.5
1000	10	1
	5	0.5

STORAGE

Chorionic Gonadotropin for Injection, USP sterile lyophilized powder should be stored at controlled room temperature (less than 25 °C) until the expiry date indicated on the label. When reconstituted, the solution should be kept refrigerated (2 °C to 8 °C) and should be used within 30 days.

Each vial of Chorionic Gonadotropin for Injection, USP contains:

Chorionic gonadotropin 10 000 USP units; mannitol 100 mg; sodium phosphate monobasic and sodium phosphate dibasic for adjustment of pH. In addition, when reconstituted with the diluent provided (Bacteriostatic Water for Injection, USP containing 0.9% benzyl alcohol), each vial contains benzyl alcohol 0.9%.

AVAILABILITY OF DOSAGE FORMS

Each package contains one vial of Chorionic Gonadotropin for Injection, USP (10 000 USP units) and one 10 mL multiple-dose vial of Sterile Diluent (Bacteriostatic Water for Injection, USP containing 0.9% benzyl alcohol).

This Prescribing Information is prepared by:

Fresenius Kabi Canada Ltd.

165 Galaxy Blvd, Suite 100
Toronto, ON M9W 0C8

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