Control # 040064

Date of Approval:
May 5, 1997

PACKAGE INSERT

Profasi® HP
chorionic gonadotropin for injection, USP
10,000 USP Units
gonadotropin

DESCRIPTION

Profasi® HP [chorionic gonadotropin for injection, USP (hCG)], extracted from the urine of pregnant women, 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.

Profasi® HP (chorionic gonadotropin for injection, USP) 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: Profasi® HP (chorionic gonadotropin for injection, USP) is given in an attempt to stimulate the interstitial cells of the testes (cells of Leydig) to produce androgen. The response to Profasi® HP may be considered similar to the effect produced 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.

Profasi® HP 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: Profasi® HP is administered in the second phase of the cycle in an attempt to maintain the functional integrity of the corpus luteum and to stimulate its secretion of progesterone. Response to Profasi® HP may be considered similar to the effect produced 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 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.

Male:

Profasi® HP (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. hCG thus may help predict whether or not orchiopexy will be needed in the future. Although, in some cases, descent following hCG administration is permanent, in most cases, the response is temporary.
   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, and 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 in some cases acceleration of longitudinal bone growth as well as sexual and somatic maturation.

4. **Hypogonadotropic Eunuchoidism.**
   Therapy is directed to the development of primary and secondary sex characteristics through the ability of chorionic gonadotropin to stimulate the interstitial cells of the testes to secrete androgen. In the patient of pubertal age, the response to Profasi® HP is usually dramatic. The adult patient does not respond as readily, but in view of the permanent effects frequently observed following Profasi® HP therapy, it is recommended that in either group, treatment be initiated with this substance, and that androgen be administered only if Profasi® HP 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 Profasi® HP will serve to establish diagnosis and indicate type of treatment required.

Lack of response to Profasi® HP therapy may be taken 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:
Profasi 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, and the administration of large daily doses of Profasi® HP may provide a beneficial luteotropic effect in the habitual aborter. Preconceptional treatment with Profasi® HP 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 inadequate for proper implantation and early development of the fertilized ovum. In such cases, chorionic gonadotropin may be used in an attempt to stimulate progesterone secretion and to encourage a return to normal ovarian function.

CONTRAINDICATIONS
Profasi® HP (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. hyperprolactinaemia, 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.
- In men, u-hCG will not be effective in cases where the FSH level is raised since this is indicative of primary testicular failure.
- Urinary-hCG is not effective and is not indicated for weight reduction.
- Precocious puberty.
- Active thrombophlebitis or thromboembolic event.
- Allergy to u-hCG.

WARNINGS

Female:

- Ovarian hyperstimulation syndrome (OHSS)

  In women undergoing ovulation induction, an excessive ovarian response to follicular stimulating agents 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 primary 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. Ovarian enlargement declines rapidly.

  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. Pelvic examination of enlarged ovaries should be gentle, in order to avoid rupture of ovarian cysts. 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. Use of diuretics should be avoided in the primary phase of the syndrome, since they may precipitate cardiovascular shock in a patient who already has plasma hypovolemia. They may however 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 be prolonged 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.

- Rupture of ovarian cysts with resultant haemoperitoneum

- Thromboembolic complications Thromboembolic events have been reported following 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 cases, thromboembolic events have resulted in death.

- Multiple pregnancy The incidence of multiple pregnancies and births is increased following 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 result might be obtained if the test is carried out in a

patient who has recently undergone (over the last 7 days) or is still having u-hCG administration.

Males:
Androgens may cause fluid retention in the male if high doses of u-hCG are administered. In such cases dosage should be considerably reduced particularly in patients with cardiac or renal disease, epilepsy, migraine or asthma.

Sexual precocity: u-hCG may cause sexual precocity when administered in young patients for cryptorchidism. If signs are observed, treatment should be stopped. If continued therapy is considered necessary, a reduced dosage regimen should be instituted.

Finally, u-hCG may induce gynecomastia.

PRECAUTIONS
Drug Interaction:
No clinically significant drug interactions have been reported during u-hCG therapy.

ADVERSE REACTIONS
The following adverse reactions have been associated with the administration of Profasi® HP (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 between treatment with fertility drugs and ovarian cancer has not been established.

DOSAGE AND ADMINISTRATION
DOSAGE:
The dosage regimen employed in any particular case will depend 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).**
   (1) 4,000 USP units, three times weekly, for two to three weeks, or (2) 1,000 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 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 Profasi® HP 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.**
   4,000 to 5,000 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).**
1,000 to 5,000 USP units three times weekly.

4. **Hypogonadotropic Eunuchoidism.**
4,000 to 5,000 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).**
4,000 to 5,000 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)
5,000 to 10,000 USP Units one day following the last dose of gonadotropins.

2. **Abortion (habitual).**
1,000 to 2,000 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 1,000 USP units Profasi® HP may be given daily from the 15th to the 24th day. An alternative schedule is 1,500 USP units every other day, three times in all, on the 16th, 18th, and 20th day of the cycle.

ADMINISTRATION:
Profasi® HP (chorionic gonadotropin for injection, USP) is FOR SUBCUTANEOUS OR INTRAMUSCULAR USE ONLY.

Preparation of Solution: Withdraw sterile air from the vial containing the lyophilized Profasi® HP and inject it into the diluent vial. Remove up to 10 mL from the diluent vial (see table below) and add to the Profasi® HP vial; agitate gently until dissolution 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.

Profasi® HP may be reconstituted by adding the required amount of diluent to obtain the desired dosage.

Table of Reconstitution and Administration Alternatives

Desired Dosage (units)	Diluent Volume Options (mL)	Injection Volume (mL)
10,000	10	10
	5	5
	2.5	2.5
	1.0	1.0
5,000	10	5
	5	2.5
	2.5	1.25
4,000	10	4
	5	2
	2.5	1
2.000	10	2
	5	1
	2.5	0.5
1,000	10	1
	5	0.5

AVAILABILITY

Each package contains one vial of Profasi® HP (10,000 USP Units) and one 10 mL multiple-dose vial of Sterile Diluent (bacteriostatic water for injection, USP containing 0.9% benzyl alcohol.)

Each vial of Profasi® HP contains:
Chorionic gonadotropin, 10,000 USP Units; mannitol, 100 mg; sodium dihydrogen phosphate and disodium phosphate 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%.

STORAGE

Profasi® HP (chorionic gonadotropin for injection, USP) sterile lyophilized powder may be stored at room temperature (15°-30°C) until the expiry date indicated on the label. When reconstituted the solution should be refrigerated (2°-8°C) and should be used within 30 days.

For more information contact:
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