SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

HuCoG HP [highly purified chorionic gonadotrophin for Injection B.P. 5000 IU]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each vial contains:

Chorionic Gonadotrophin B.P. ..... 5000 I.U.

Qualitative and quantitative composition of HuCoG HP

Names of Ingredients	**Unit**	**Function**	**Reference to Standards**
Active Substance(s)			
Human Chorionic Gonadotrophin (HP)	5000 I.U.	Active ingredient	B.P.
Excipient(s)			
Anhydrous Disodium Hydrogen Phosphate	1.42mg	Buffer	B.P.
Sucrose	10.0mg	Stabilizer	B.P.
Mannitol	30.0mg	Bulking Agent	B.P.
Sodium Ascorbate	0.1mg	Antioxidant	B.P.
Phosphoric acid	q.s	pH adjustment	B.P.
Sodium hydroxide	q.s	pH adjustment	B.P.

BP: British Pharmacopoeia

3. PHARMACEUTICAL FORM:

Dosage form: Freeze dried powder for Injection.

Description: A white or almost white, amorphous powder or cake.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications

1. *In Females*

Sterility due to the absence of follicle-ripening or ovulation.

In combination with Follicle stimulating hormone (FSH) or human menopausal gonadotropin (HMG), promotion of controlled superovulation in medically assisted reproduction programmes.

2. *In Males*

Hypogonadotrophic hypogonadism.

Delayed puberty associated with insufficient gonadotrophic pituitary function. Sterility in selected cases of deficient spermatogenesis.

4.2. Posology and method of administration

HuCoG HP is given by subcutaneous / intramuscular injection only.

In Females:

Sterility due to the absence of follicle-ripening or ovulation.

HuCoG HP 5000 is administered following the last dose of HMG Inj. or other drugs used for stimulation in infertility.

In combination with FSH or HMG, promotion of controlled superovulation in medically assisted reproduction programmes.

5000 IU HCG 30 - 40 hours after the last FSH or HMG injection

In Males:

Hypogonadotrophic hypogonadism:

HuCoG HP 5000 IU, is administered intramuscularly 2-3 times weekly.

Cases of deficient spermatogenesis.

Usually, 3,000 IU HCG per week in combination with an FSH or HMG preparation. This treatment should be continued for at least three months before any improvement in spermatogenesis can be expected. During this treatment testosterone replacement therapy should be suspended. Once achieved, the improvement may sometimes be maintained by HCG alone.

Delayed puberty associated with insufficient gonadotrophic pituitary function.

1,500 IU HCG twice weekly for at least 6 months.

Method of administration

HuCoG HP is given by subcutaneous / intramuscular injection only. The injection should be reconstituted with Sodium Chloride Injection B.P. provided with the package, immediately prior to use.

4.3. Contraindications:

- Tumors of hypothalamus, pituitary glands
- Ovarian, uterine or mammary carcinoma.
- Vaginal bleeding of unknown cause
- In males, if there are prostate or breast carcinoma.
- History of hypersensitivity to any gonadotrophins or excipients

4.4. Special warnings and precautions for use

In males and females:

Hypersensitivity reactions:

Hypersensitivity reactions, both generalised and local; anaphylaxis; and angioedema have been reported. If a hypersensitivity reaction is suspected, discontinue HuCoG® HP and assess for other potential causes for the event.

General:

HuCoG HP should not be used for body weight reduction. HCG has no effect on fat metabolism, fat distribution or appetite.

Additionally, in females:

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.

Prior to treating patients for inadequate endogenous stimulation of the gonads, an examination should be performed to exclude anatomical abnormalities of the genital organs or nongonadal endocrinopathies (e.g. thyroid or adrenal disorders, diabetes). Primary ovarian failure should be excluded by the determination of gonadotrophin levels.

Multi-fetal gestation and birth:

In the pregnancies occurring after induction of ovulation with gonadotrophic preparations, there is an increased risk of abortion and multiplets. Multiple pregnancy, especially high order, carries an increased risk in adverse maternal and perinatal outcomes. The parents should be advised of the potential risks of multiple pregnancies before starting treatment.

Congenital M*alformations:*

The incidence of congenital malformations after ART, may be higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and an increased incidence

of multiple gestations.

Vascular Complications:

Thromboembolic events, both in association with and separate from OHSS, have been reported following treatment with gonadotropins, including HuCoG® HP. 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 gonadotrophins. 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.

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.

Medical examinations:

For up to ten days after administration of HuCoG® HP, a pregnancy test may give a false- positive result.

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, dyspnoea, 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 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 HuCoG® HP. 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 10000 IU of urinary HCG for triggering final oocyte maturation, e.g. 5000 IU urinary HCG or 250 micrograms rec-HCG (which is equivalent to approximately 6500 IU of urinary HCG);
- cancel the fresh embryo transfer and cryopreserve embryos;
- avoid administration of HCG for luteal phase support.

- Adherence to the recommended HuCoG® HP 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 HuCoG® HP. 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.

Additionally, in males:

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 or migraine (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.

Male paediatric patient:

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

4.5. Interaction with other medicinal products and other forms of interaction:

No drug/drug interaction studies have been conducted with HuCoG® HP in humans. Concomitant use of HuCoG HP Injection with other agents used to stimulate ovulation (e.g. HMG, clomiphene citrate) may potentiate the follicular response. (See Warnings Precaution & Overdosage.)

4.6. Use in pregnancy and lactation:

HuCoG HP should not be given if pregnancy is suspected or to lactating mothers. It is used for luteal support.

4.7. Effects on ability to drive and use machines

No effects on ability to drive and use machines have been seen with hCG.

4.8. Undesirable effects

System Organ Class	**Signs and symptoms**
Common	
General disorders and administrative site conditions	Reactions at the site of injection- bruising, pain, redness, swelling and itching. Oedema, tiredness
Rare	
Immune system disorders	Generalized rash or fever
Nervous system disorders	Headache
Psychiatric disorders	Mood changes
Reproductive system and breast disorders	Mild OHSS- Abdominal pain and gastrointestinal symptoms such as nausea and diarrhoea, Painful breasts, mild to moderate enlargement of ovaries and ovarian cysts Severe OHSS- ascites, large ovarian cyst, weight gain, acute abdominal pain, hydrothorax, Rarely, thromboembolism has been associated with FSH/ HCG therapy.
Uncommon	
In males	
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
Reproduction system and breast disorders	HCG treatment may sporadically cause gynaecomastia.
Skin and subcutaneous tissue disorders	Acne may occur occasionally during hCG therapy.

4.9. Overdoses

The effect of an overdose is unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur. There is no antidote for overdosing. The symptoms due to overdose should be treated.

5. CLINICAL PHARMACOLOGY:

Pharmacotherapeutic group: Gonadotrophins: ATC code G03GA01

5.1. Pharmacodynamic properties

HuCoG HP is human chorionic gonadotrophin obtained from the urine of pregnant women. It stimulates the steroidogenesis in the gonads by virtue of a biological effect similar to that of LH (Luteinizing hormone, which is the same as interstitial cell stimulating hormone).

In the male, it promotes the production of testosterone and in the female the production of estrogens and particularly of progesterone after ovulation. In certain cases, this preparation is used in combination with human menopausal gonadotrophin (HMG).

Mechanism of action

HuCoG HP is a preparation of human chorionic gonadotrophin obtained from the urine of pregnant women. It stimulates the steroidogenesis in the gonads by virtue of a biological effect similar to that of LH. In the male it promotes the production of testosterone and in the female the production of estrogens and particularly of progesterone after ovulation. In certain cases, this preparation is used in combination with HMG.

5.2. Pharmacokinetic Properties

From the literature, in a study performed in healthy male subjects, maximal HCG plasma levels were reached after a single IM or SC injection of HCG at approximately six and sixteen hours respectively; in addition, maximum

concentrations and areas under the concentration curves were higher after the IM than after the SC injection. However, these differences did not translate into significant differences in terms of testicular steroidogenic response.

In a study performed in female subjects under oral contraceptives, IM and SC administration of HCG were found to be bioequivalent regarding the extent of absorption and the apparent elimination half-lives of approximately 33 hours; maximal HCG plasma levels were reached after approximately 20 hours regardless of the route of administration. Although high intersubject variability was observed, the difference related to gender after IM injection may be caused by gluteal fat thickness in women which exceeds that in men. In another study performed in female patients in the early follicular phase of their menstrual cycle, the bioavailability of a single dose of hCG was higher with the IM route than with the SC route and lower in obese women than in non-obese women.

HCG is approximately 80 per cent metabolized, predominantly in the kidneys.

On basis of the recommended dose regimens and elimination half-life, accumulation is not expected to occur.

5.3. Preclinical safety data

No relevant data available

6. Pharmaceutical Particulars :

6.1. List of excipients:

- Anhydrous Disodium Hydrogen Phosphate
- Sucrose
- Mannitol
- Sodium Ascorbate
- Phosphoric Acid
- Sodium hydroxide

6.2. Incompatibilities:

The product is stable and there is no incompatibility amongst excipients.

6.3. Shelf life:

36 months.

6.4. Special precautions for storage:

Vials of HuCoG 5000 HP should be stored between 2°C - 8°C. Do not freeze. Protect from light. Reconstituted solution should be used immediately after preparation at 20C - 80C, any unused portion should be discarded.

6.5. Nature and contents of container:

HuCoG HP is supplied in vial containing sterile, freeze dried white powder having activity of 5000 I.U. Each vial is accompanied by an ampoule with the protective sleeve containing 1 ml of sodium chloride Injection B.P. as diluent in a carton along with pack insert and an ampoule breaking manual.

6.6 Special precautions for disposal

Not applicable

7. APPLICANT/MANUFACTURER:

Applicant:

Bharat Serums & Vaccines Ltd.
3rd Floor, Liberty Tower, Plot No. K-10,
Behind Reliable Plaza, Kalwa Industrial Estate, Airoli,
Navi Mumbai 400708

Manufactured by:

Bharat Serums and Vaccines Limited.
Plot No. K-27, Anand Nagar, Jambivili Village,
Additional M.I.D.C., Ambernath East- 421506,
Maharashtra State, India.