1. NAME OF THE MEDICINAL PRODUCT

Pregnyl ® 5000 I.U. powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pregnyl consists of a freeze-dried powder for injection. The active ingredient [human chorionic gonadotrophin (hCG)] which is obtained from the urine of pregnant women, has luteinizing hormone (LH) activity.

An ampoule contains 5000 I.U. hCG.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection. The powder is a white, dry powder or cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the female
Sterility due to the absence of follicle-ripening or ovulation.
In combination with FSH or HMG, promotion of controlled superovulation in medically assisted reproduction programmes.

In the male
Hypogonadotrophic hypogonadism.
Delayed puberty associated with insufficient gonadotrophic pituitary function.
Sterility in selected cases of deficient spermatogenesis.

4.2 Posology and method of administration

Posology

In the female
Sterility due to the absence of follicle-ripening or ovulation.
5,000–10,000 IU hCG to induce ovulation, following treatment with an FSH (Follicle Stimulating Hormone) or HMG (Human Menopausal Gonadotrophins) preparation.

In combination with FSH or HMG, promotion of controlled superovulation in medically assisted reproduction programmes.
5,000–10,000 IU hCG 30 - 40 hours after the last FSH or HMG injection. Pregnyl should not
be administered if the following criteria have not been met: at least 3 follicles greater than 17mm in diameter are present with 17ß estradiol levels of at least 3500 pmol/L (920 picogram/ml). Oocyte collection is carried out 32 - 36 hours after the hCG injection.

As luteal phase support, two to three injections of 1,000 to 3,000 IU hCG each may be given within nine days of ovulation or embryo transfer, for example on day 3, 6 and 9 after ovulation induction or embryo transfer.

In the male
Hypogonadotrophic hypogonadism.
500–1,000 IU hCG 2-3 times weekly.

Delayed puberty associated with insufficient gonadotrophic pituitary function.
1,500 IU hCG twice weekly for at least 6 months.

Sterility in selected 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.

Method of Administration

After addition of the solvent to the freeze-dried substance, the solution should be given immediately by intramuscular or subcutaneous injection. Any unused solution should be discarded. Subcutaneous injection may be carried out by patient or partner, provided that proper instruction is given by the physician. Self administration of Pregnyl should only be performed by patients who are well- motivated, adequately trained and with access to expert advice.

4.3 Contraindications

In males and females:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. (see section 4.4).
- Known or suspected sex hormone-dependent tumors of the ovary, breast, uterus, testis, prostate, pituitary gland or hypothalamus.

Additionally in females:

- Malformations of the reproductive organ that contraindicate pregnancy.
- Fibroid tumours in the uterus that contraindicate pregnancy.
- Abnormal (not menstrual) vaginal bleeding without a known/diagnosed cause.

4.4 Special warnings and precautions for use

4.4 Special warnings and precautions for use

In 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 section 4.3)

General:

- Patients should be evaluated for uncontrolled non-gonadal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders) and appropriate specific treatment given.
- The active ingredient of this preparation is extracted from human urine. Therefore, the risk of a transmission of a pathogen (known or unknown) cannot be excluded. No cases of viral contamination associated with administration of gonadotropin extracted from human urine have been reported.
- Patients on a controlled sodium diet: This medicinal product contains less than 1 mmol sodium (23 mg) per daily dose, i.e. essentially “sodium-free”.
- Pregnyl should not be used for body weight reduction. HCG has no effect on fat metabolism, fat distribution or appetite.

Additionally in females:

Multi-fetal gestation and birth:

- In pregnancies occurring after induction of ovulation with gonadotropic preparations, there is an increased risk of a 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 ART as well as in anovulatory patients are higher than in the normal population.

Congenital Malformations:

- The incidence of congenital malformations after ART as well as in anovulatory patients may be slightly 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 risk of multiple gestations. There are no signs that the use of gonadotropins in ART is associated with an increased risk of congenital defects.

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.

**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 pediatric patients:**

- 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 interaction studies have been performed; 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.

### 4.6 Fertility, Pregnancy and lactation

Not applicable.

### 4.7 Effects on ability to drive and use machines

As far as known Pregnyl has no influence on the ability to drive and use machines.

### 4.8 Undesirable effects

Frequency is unknown for all undesirable effects described below (cannot be determined with available data).

**Immune system disorders**

In rare cases generalized rash or fever may occur.
General disorders and administrative site conditions
Local site reactions such as bruising, pain, redness, swelling and itching. Oedema. Occasionally allergic reactions have been reported, mostly manifesting as pain and/or rash at the injection site. Tiredness.

Nervous system disorders
Headache.

Psychiatric disorders
Mood changes.

In the female
Reproductive system and breast disorders
Unwanted ovarian hyperstimulation, mild or severe ovarian hyperstimulation syndrome (OHSS, see section 4.4):

Mild OHSS:  Painful breasts
  Mild to moderate enlargement of ovaries
  Ovarian cysts
  Abdominal pain
  Abdominal discomfort
  Gastrointestinal symptoms such as nausea, diarrhoea and bloating

Severe OHSS:  Large ovarian cysts (prone to rupture), Acute abdominal pain
  Ascites
  Weight gain
  Hydrothorax
  In rare instances, thromboembolism has been associated with FSH/hCG therapy

Not all symptoms described are always associated to 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.

Reproduction system and breast disorders
HCG treatment may sporadically cause gynaecomastia.

Skin and subcutaneous tissue disorders
Acne may occur occasionally during hCG therapy.
Reporting of suspect adverse reactions
Reporting suspect adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspect adverse reactions via the Yellow Card scheme, at www.mhra.gov.uk/yellowcard.

4.9 Overdose

The toxicity of human chorionic gonadotrophic hormone is very low. However, too high a dose may lead to hyperstimulation of the ovaries. (See "Unwanted Hyperstimulation").

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: gonadotrophins: ATC code G03G A01

Pregnyl 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 (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).

Because HCG is of human origin, no antibody formation is to be expected.

5.2 Pharmacokinetic properties

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

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for injection contains:

Carmellose sodium
Mannitol (E421)
Disodium phosphate (anhydrous)
Sodium dihydrogen phosphate (anhydrous)

6.2 Incompatibilities

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

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in refrigerator (2°C to 8°C). Do not freeze. Keep the ampoules in the outer carton to protect from light.

6.5 Nature and contents of container

2ml ampoule containing freeze-dried powder with 1ml ampoule of solvent (sodium chloride 9mg/ml)
Pregnyl is available in packs of 1, 3 or 10 ampoules of powder and solvent. Not all pack sizes may be marketed.
In correspondence please quote batch number.
6.6 Special precautions for disposal

Pregnyl should be reconstituted with the solvent provided. Do not use if the solution contains particles or if the solution is not clear. Since an opened ampoule cannot be resealed in such a way to further guarantee the sterility of the contents, the solution should be used immediately after reconstitution. Discard any remaining solution after single use.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Organon Laboratories Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 0FL
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00065/5079R

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25/02/1991 / 24/03/2003

10 DATE OF REVISION OF THE TEXT

09/06/2017