# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

PREGNYL 5000 I.U., powder and solvent for solution for injection.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

An ampoule contains 5,000 IU hCG

The reconstituted solution contains 5000 IU hCG per mL.

Excipient with known effect: sodium. This medicinal product contains less than 1 mmol sodium (23 mg) per daily dose, i.e. essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is a white, dry powder or cake. The solvent is a clear and colourless aqueous solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

In the female:
- Ovulation induction in subfertility due to anovulation or impaired follicle-ripening.
- Preparation of follicles for puncture in controlled ovarian hyperstimulation programs (for medically assisted reproductive techniques).
- Luteal phase support.

In the male:
- Hypogonadotropic hypogonadism (also cases of idiopathic dysspermias have shown a positive response to gonadotropins).
- Delayed puberty associated with insufficient gonadotropic pituitary function.
- Cryptorchidism, not due to anatomical obstruction.
- Preoperative preparation of ectopic testes

### 4.2 Posology and method of administration

Dosage
Dosage in females:
- Ovulation induction in subfertility due to anovulation or impaired follicle-ripening
  Usually, one injection of 5 000-10 000 IU Pregnyl to complete treatment with an FSH-containing preparation.
- Preparation of follicles for puncture in controlled ovarian hyperstimulation programs
  Usually, one injection of 5 000-10 000 IU Pregnyl to complete treatment with an FSH-containing preparation.
- Luteal phase support
  Two to three repeat injections of 1000 to 3000 IU each may be given within nine days following ovulation or embryo transfer (for example on day 3, 6 and 9 after ovulation induction).

Dosage in males:

- Hypogonadotropic hypogonadism
  1000-2000 IU Pregnyl, two to three times per week. If the main complaint is subfertility, Pregnyl may be given with an additional follitropin (FSH)-containing preparation two to three times a week. 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 gonadotropic pituitary function
  1500 IU two to three times a week for at least six months.
- Preoperative preparation of ectopic testes
  500 IU 2 or 3 times weekly for 1 to 2 months before operation
- Cryptorchidism, not due to anatomical obstruction
  -under 2 years of age: 250 IU twice weekly for six weeks,
  -under 6 years of age: 500-1000 IU twice weekly for six weeks,
  -over 6 years of age: 1500 IU twice weekly for six weeks.
  If necessary, this treatment can be repeated.

Method of administration
After addition of the solvent to the freeze-dried substance, the reconstituted Pregnyl solution should be slowly administered intramuscularly or subcutaneously.

## 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 tumours, such as ovary, breast and uterine carcinoma in female and prostatic or breast carcinoma in the male.

*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

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 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.
- 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 are higher than in the normal population.

Congenital Malformations:

- The incidence of congenital malformations after ART 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 ART. There are no indications that the use of gonadotrophins during ART is associated with an increased risk of congenital malformations.

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.

Medical examinations:
For up to 10 days after administration of Pregnyl, a pregnancy test may give a false-positive result.

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.
- hCG should be used cautiously in prepubertal boys to avoid premature epiphyseal closure or precocious sexual development. Use should cease immediately in such cases. Skeletal maturation should be monitored regularly. A growth spurt may also be associated with use and this should be kept in mind particularly where epiphyseal growth is still potentially active.

The product should be used with caution in patients with an allergic diathesis. A preliminary skin test may be of assistance in detecting hypersensitivity.

This product should only be used under the supervision of a specialist, for the first administration, having available adequate facilities for appropriate laboratory monitoring.

**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’

## 4.5 Interaction with other medicinal products and other forms of interaction

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

## 4.6 Fertility, pregnancy and lactation

Pregnyl may be used for luteal phase support, but should not be used later on in pregnancy. It must not be used during lactation.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Immune system disorders
In rare cases generalized rash or fever may occur.

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.

*In the female:*

Vascular disorders
In rare instances, thromboembolism has been associated with FSH/hCG therapy, usually associated with severe OHSS (see also section 4.4).

Respiratory, thoracic and mediastinal disorders
Hydrothorax, as a complication of severe OHSS.

Gastrointestinal disorders
Abdominal pain and gastrointestinal symptoms such as nausea and diarrhea, related to mild OHSS. Ascites, as a complication of severe OHSS.

Reproductive system and breast disorders
Unwanted ovarian hyperstimulation, mild or severe ovarian hyperstimulation syndrome (OHSS, see section 4.4). 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.

Investigations
Weight gain as a characteristic of 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 gynaecomastia.

Reporting of suspected adverse reactions

Reporting suspected 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 suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

## 4.9 Overdose

The acute toxicity of urinary gonadotropin preparations has been shown to be very low. Nevertheless, there is a possibility that too high a dosage of hCG may lead to ovarian hyperstimulation syndrome (OHSS; see section 4.4).

## 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: gonadotropins: ATC code G03G A01

Pregnyl contains hCG which has LH activity. LH is indispensable in normal female and male gamete growth and maturation, and gonadal steroid production.

*In the female:*
Pregnyl is given as a substitute for the endogenous mid-cycle LH surge to induce the final phase of follicular maturation, leading to ovulation. Pregnyl is also given as a substitute for endogenous LH during the luteal phase.

*In the male:*
Pregnyl is given to stimulate Leydig cells to promote the production of testosterone.

## 5.2 Pharmacokinetic properties

Maximal hCG plasma levels will be reached in males approximately six and sixteen hours after a single IM or SC injection of hCG respectively, and in females after approximately 20 hours. 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. HCG is for approximately 80 per cent metabolized, predominantly in the kidneys. IM and SC administration of hCG were found to be bioequivalent regarding the extent of absorption and the apparent elimination half-lifes of approximately 33 hours. On basis of the recommended dose regimens and elimination half-life, cumulation is not expected to occur.

## 5.3 Preclinical safety data

No particulars.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Powder for solution for injection

Carmellose sodium
Mannitol
Disodium phosphate dihydrate
Sodium dihydrogen phosphate dihydrate

*Solvent for Parenteral use*

Sodium chloride
Sodium hydroxide for pH adjustment.
Concentrated hydrochloric acid for pH adjustment.
Water for injections

## 6.2 Incompatibilities

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

## 6.3 Shelf life

3 years.

## 6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Keep the ampoules in the outer carton in order to protect from light.

## 6.5 Nature and contents of container

Packs of one or ten 2 ml ampoules of colourless (Type I) glass, containing powder for injection corresponding to 5000 IU hCG and one or ten packs of 1 ml ampoules of colourless glass (Type I), containing the solvent for parenteral use.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The powder for injection is reconstituled by adding the solvent.

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.

Do not use if the solution contains particles.

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

# 7 MARKETING AUTHORISATION HOLDER

NV Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

# 8 MARKETING AUTHORISATION NUMBER

PA0964/005/002

# 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1979

Date of last renewal: 28th February 2008

# 10 DATE OF REVISION OF THE TEXT

April 2018