Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

PREGNYL 1500 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 1500 IU hCG.

The reconstituted solution contains 1500IU hCG per mL.

For a full list of excipients, see 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 the female:
- 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 the male:
- 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.

4.3 Contraindications

- Hypersensitivity to human gonadotropins or any of the excipients.
- Known or suspected sex hormone-dependent tumours, such as ovary, breast and uterine carcinoma in female and prostatic or breast carcinoma in the male.
- Malformations of the sexual organs incompatible with pregnancy
- Fibroid tumours of the uterus incompatible with pregnancy

4.4 Special warnings and precautions for use

In the female:

- In pregnancies occurring after induction of ovulation with gonadotropic preparations, there is an increased risk of multiplets.
- 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 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.
- The incidence of congenital malformations after Assisted Reproductive Technologies (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.
- 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 Pregnyl 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, diarrhoea), 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.

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

In the male:
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 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.
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

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 alertness and concentration.

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.
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.

Investigation
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

One 2ml ampoule of colourless (Type I) glass containing powder for injection corresponding to 1500 IU hCG and one 1ml ampoule of colourless glass (Type I) containing the solvent.

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 unopened 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

PA 964/5/1

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

May 2015