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N.V. Organon, a part of Schering-
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ORGANON STANDARD SmPC OF Pregnyl

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1. NAME OF THE MEDICINAL PRODUCT

Pregnyl 500, 1500, 5000 IU 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 luteinizing hormone (LH) activity.

An ampoule contains 500, 1500 or 5000 IU hCG.

For 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.

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4.2 Posology and method of administration

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.
- 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.

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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 multiples.
- 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

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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

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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. Skeletal maturation should be monitored regularly.

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 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.

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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.

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.

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).

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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-lives 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.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The powder for injection contains mannitol, disodium hydrogen phosphate, sodium dihydrogen phosphate and sodium carboxymethylcellulose.

The ampoule of solvent contains sodium chloride (9 mg) and water for injections (1 ml).

6.2 Incompatibilities

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

6.3 Shelf life

The shelf-life of Pregnyl is 3 years.

Pregnyl may be used until the expiration date indicated on the package

6.4 Special precautions for storage

Pregnyl should be stored in the dark between 2 °C and 15 °C.

6.5 Nature and contents of container

Ampoules of Pregnyl 500 IU, 1500 IU and 5000 IU contain powder for injection corresponding to 500, 1500 and 5000 IU hCG, respectively.

6.6 Instructions for use and handling <and disposal>

The powder for injection is reconstituted by adding the solvent.

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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.

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

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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