AUSTRALIAN PRODUCT INFORMATION

PREGNYL®

(human chorionic gonadotrophin)
Powder for Injection

1 NAME OF THE MEDICINE

Human chorionic gonadotrophin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pregnyl is a preparation of human chorionic gonadotrophin (hCG) obtained from the urine of pregnant women.

Each vial of Pregnyl powder for injection contains 1500 IU or 5000 IU human chorionic gonadotrophin.

Each mL of the reconstituted Pregnyl 1500 IU solution contains 1500 IU of human chorionic gonadotrophin (hCG).

Each mL of the reconstituted Pregnyl 5000 IU solution contains 5000 IU of human chorionic gonadotrophin (hCG).

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

Powder for injection.

Powder for injection: White to almost white amorphous powder.

Diluent: Clear colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

In the female:

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

In the male:

- Hypogonadotrophic hypogonadism.
- Delayed puberty associated with insufficient gonadotrophic pituitary function.
- Cryptorchism, not due to an anatomic obstruction.
- Sterility, in selected cases of deficient spermatogenesis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

In the female:
Sterility due to the absence of follicle-ripening or ovulation: usually, 5000-10000 IU to complete treatment with a FSH containing preparation. A repeat injection of 5000 IU may be given 7 days later (or in accordance with individual patient needs) to prevent insufficiency of the corpus luteum.

In the male:

- Hypogonadotrophic hypogonadism:
  500-1000 IU 2-3 times per week.
- Delayed puberty associated with insufficient gonadotrophic pituitary function:
  1500 IU twice weekly for at least 6 months.
- Cryptorchism, not due to an anatomic obstruction:
  Under 6 years of age: 500 IU twice weekly for 6 weeks.
  Over 6 years of age: 1000 IU twice weekly for 6 weeks.
  If necessary, this treatment can be repeated.
- Sterility in selected cases of deficient spermatogenesis:
  Usually, 3000 IU per week in combination with a FSH containing preparation.

Method of Administration

Reconstitution
Do not use if the solution contains particles or if the solution is not clear.

After addition of the solvent to the freeze-dried substance, the reconstituted Pregnyl solution should be administered intramuscularly. The solution should be used immediately after reconstitution.

4.3 CONTRAINDICATIONS

- Hypersensitivity to human gonadotrophins or any of the ingredients in Pregnyl (see **Section 4.4 Special Warnings and Precautions for Use**).
- Known or suspected sex hormone-dependent tumours, such as ovary, breast and uterine carcinoma in female and prostatic carcinoma or mammary carcinoma in the male.
- Malformations of the reproductive organs incompatible with pregnancy.
- Fibroid tumours of the uterus incompatible with pregnancy.
- Abnormal (not menstrual) vaginal bleeding without a known/diagnosed cause.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The active ingredient of this preparation is extracted from human urine. Therefore the risk of a transmission of a pathogen (known or unknown) can not be completely excluded.

For 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 Contraindications**).

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.

In the female:

Multi-foetal gestation and birth:

- In pregnancies occurring after induction of ovulation with gonadotrophic preparations, there is an increased risk of 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 normal population.

Congenital malformations:

- 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.

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, diarrhoea, 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, haematological 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.

  Adherence to the recommended Pregnyl dose and treatment regimen is advised. Care should be taken with the administration of Pregnyl because OHSS may be triggered by administration of human Chorionic Gonadotrophin (hCG). OHSS may also be triggered by pregnancy (endogenous hCG). Early OHSS usually occurs within 10 days after hCG administration and may be associated with an excessive ovarian response to gonadotrophin 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.

Follow current clinical practice for reducing the risk of OHSS during Assisted Reproductive Technology (ART). Careful monitoring of ovarian response is important to reduce the risk of OHSS. To monitor 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. For patients at increased risk of OHSS or if OHSS develops, standard and appropriate management of OHSS should be implemented and followed.

Ovarian torsion:

- Ovarian torsion has been reported after treatment with gonadotrophins, 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 gonadotrophins, 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 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.

In the male:

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

- Patients with latent or overt cardiac failure, 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.

Use in renal impairment

In the male: patients with renal dysfunction (or a history of this condition) should be kept under close medical supervision, since aggravation or recurrence may occasionally be induced as a result of increased androgen production.

Use in the elderly

No data available.

Paediatric use

See **Section 4.2 Dose and Administration, In the male.**

Effects on laboratory tests

See **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions.**

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 10 days with the immunological determination of serum/urinary hCG, leading to a false positive pregnancy test.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See **Section 4.1 Therapeutic Indications.**

Use in pregnancy

Category A

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

Use in lactation

Pregnyl must not be used during lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As far as is known this medicine has no influence on alertness and concentration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Immune system disorders
In rare cases generalised 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 **Section 4.4 Special Warnings and Precautions for Use**).

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

Gastrointestinal disorders
Abdominal pain and gastrointestinal symptoms such as nausea and diarrhoea, 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 Special Warnings and Precautions for Use**).

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 suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The acute toxicity of urinary gonadotrophin 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 Special Warnings and Precautions for Use**).

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Human chorionic gonadotrophin (hCG) stimulates steroidogenesis in the gonads by virtue of a biologic effect similar to that of LH (luteinising 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 a follicle stimulating hormone (FSH) containing preparation. Because hCG is of human origin, no antibody formation is to be expected.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution

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.

Metabolism

HCG is approximately 80% metabolised, predominantly in the kidneys.

Excretion

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

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder for injection: carmellose sodium, monobasic sodium phosphate dihydrate, dibasic sodium phosphate dihydrate, and mannitol.

Diluent: 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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

The contents of the vial should be used immediately after reconstitution.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

Both Pregnyl powder for injection and the diluent are available in glass (Type 1 clear) vials.

Pack sizes:
Pregnyl 1500 IU: 3 vials of powder for injection and 3 vials of diluent.
Pregnyl 5000 IU: 1 vial of powder for injection and 1 vial of diluent; 3 vials of powder for injection and 3 vials of diluent*.

*Pack size not currently marketed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number

9002-61-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
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9 DATE OF FIRST APPROVAL

20 September 1991

10 DATE OF REVISION

30 June 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI Format Update as per Form for Providing PI 8 Mar 2018
4.4	• Revised subsection “Ovarian Hyperstimulation Syndrome (OHSS)” • Replaced text that describes clinical measures to be considered to reduce the risk of OHSS with language to direct the healthcare provider to follow current clinical practice for reducing the risk of OHSS during Assisted Reproductive Technology (ART).
5.2	Addition of pharmacokinetic information as part of PI format update

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