

Gonagen™

Human Menopausal Gonadotrophin (Menotrophin BP) for Injection

DESCRIPTION

Gonagen™ is a preparation of menotrophin (human menopausal gonadotrophin, HMG) which belongs to a group of medicines called gonadotrophins. Menotrophin is a highly purified mixture of two hormones called follicle stimulating hormone (FSH) and luteinizing hormone (LH). The FSH and LH in **Gonagen™** are obtained from the urine of postmenopausal women. **Gonagen™** which contains both FSH and LH activity induces ovarian follicular growth and development as well as gonadal steroid production in women who do not have ovarian failure. FSH is the primary driver of follicular recruitment and growth in early folliculogenesis, while LH is important for ovarian steroidogenesis and is involved in the physiological events leading to development of a competent pre-ovulatory follicle. Follicular growth can be stimulated by FSH in the total absence of LH, but resulting follicles develop abnormally and are associated with low estradiol levels and inability to luteinize to a normal ovulatory stimulus. In line with the action of LH activity in enhancing steroidogenesis, estradiol levels associated with treatment of **Gonagen™** are higher than with recombinant FSH preparations. This should be considered when monitoring patient's response based on estradiol levels. In the male, the maintenance of testicular testosterone (T) production and spermatogenesis is regulated by the two pituitary gonadotrophins, luteinizing hormone (LH) and follicle stimulating hormone (FSH). The testicular target cells of LH are the Leydig cells present in the interstitial space, and those of FSH are the Sertoli cells present in the seminiferous tubules. LH stimulates Leydig cell T production, and FSH stimulates in Sertoli cells, in synergy with T, the production of regulatory molecules and nutrients needed for the maintenance of spermatogenesis. Hence, both testosterone (T) and FSH regulate spermatogenesis indirectly through Sertoli cells.

INDICATIONS

In women, **Gonagen™** is used to treat infertility in the following two situations:

- To promote the release of eggs from the ovaries (ovulation) in women who are not ovulating, including with polycystic ovarian disease, and who have not responded to treatment with another medicine called clomiphene citrate.
 - To help multiple follicles and therefore eggs to develop in women having Assisted Reproductive Technology (ART) like in vitro fertilization (IVF) treatment or other types of 'assisted conception'. The eggs are then harvested and fertilized outside the body.
- In men, **Gonagen™** is used to treat infertility in the following situation:
- Low sperm count (oligospermia).

DOSAGE AND ADMINISTRATION

Gonagen™ is intended for subcutaneous (S.C.) or intramuscular (I.M.) injection after reconstitution with 0.9% sodium chloride injection. The powder should be reconstituted immediately prior to use.

In women:

(i) Women who are not ovulating (not producing eggs):

Gonagen™ therapy should be started within the initial 7 days of the menstrual cycle. The recommended initial dose of **Gonagen™** is 75 - 150 IU daily, which should be maintained for at least 7 days. Based on routine clinical monitoring (including ovarian ultrasound, preferably in combination with measurement of estradiol levels) subsequent treatment should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than every 7 days. The recommended dose increment is 37.5 IU per adjustment, and should not exceed 75 IU (maximum 75 IU). The maximum daily dose should not be higher than 225 IU. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should commence treatment at a higher starting dose than in the abandoned cycle.

When an optimal stimulation is obtained, a single injection of 5,000 IU to 10,000 IU hCG should be given 1 day after the last **Gonagen™** injection. The patient is recommended to have sexual intercourse on the day of and the day following hCG administration. Alternatively, intrauterine insemination (IUI) may be performed. If an excessive response to **Gonagen™** is obtained, treatment should be stopped and hCG withheld and the patient should use a barrier method of contraception or refrain from having sexual intercourse until the next menstrual bleeding has started.

(ii) Women in assisted reproductive technology programs:

In a protocol using downregulation with a GnRH agonist, **Gonagen™** therapy should start approximately 2 weeks after the start of agonist treatment.

In a protocol using downregulation with a GnRH antagonist, **Gonagen™** therapy should start on day 2 or 3 of the menstrual cycle.

The recommended initial dose of **Gonagen™** is 150 - 225 IU daily for at least the first 5 days of treatment. Based on routine clinical monitoring (including ovarian ultrasound, in combination with measurement of estradiol levels) subsequent treatment should be adjusted according to individual patient response, and should not exceed more than 150 IU per adjustment. The maximum daily dose given should not be higher than 450 IU daily and in most cases dosing beyond 20 days is not recommended.

When an optimal response is obtained, a single injection of 5,000 up to 10,000 IU hCG should be administered to induce follicular maturation in preparation for oocyte retrieval. Patients should be followed closely for at least 2 weeks after hCG administration. If an excessive response to **Gonagen™** is obtained, treatment should be stopped and hCG withheld and the patient should use a barrier method of contraception or refrain from having sexual intercourse until the next menstrual bleeding has started.

In men:

For low sperm count:

- The usual dose is 75 or 150 IU two or three times a week.
- Treatment is normally continued for at least 3 or 4 months.

CONTRAINDICATIONS

Human menopausal gonadotrophin (menotrophins) is contraindicated who exhibit:

- Prior hypersensitivity to HMG or menotrophins products.
 - Tumors of pituitary gland or hypothalamus.
- Also contraindicated in women who exhibit:**
- High levels of FSH indicating primary ovarian failure
 - Pregnancy
 - Presence of uncontrolled non-gonadal endocrinopathies
 - Sex hormone dependent tumors of the reproductive tract and accessory organ
 - Abnormal uterine bleeding of undetermined origin
 - Ovarian cyst or enlargement of undetermined origin, not due to polycystic ovary syndrome
- Contraindicated in men who exhibit:**
- Carcinoma of the prostate.
 - Tumor of the testicles.

SIDE EFFECTS

The most common adverse reactions include: abdominal cramps; abdomen enlarged; abdominal pain; headache; nausea, vomiting, diarrhea, injection site pain and reaction; injection site inflammation; Ovarian Hyperstimulation Syndrome (OHSS)

PRECAUTIONS AND WARNINGS

To minimize the hazards associated with abnormal ovarian enlargement that may occur with HMG therapy, treatment should be individualized and the lowest effective dose should be used. If there is evidence that Ovarian Hyperstimulation Syndrome (OHSS) may be developing prior to hCG administration, the hCG should be withheld. If severe OHSS occurs, treatment must be stopped and the patient should be hospitalized. In addition, thromboembolic events, both in association with, and separate from, Ovarian Hyperstimulation Syndrome (OHSS) have been reported following menotrophins therapy. Intravascular thrombosis and embolism, which may originate in venous or arterial vessels, can result in reduced blood flow to critical organs or the extremities, sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. Ovarian torsion has been reported after treatment with gonadotrophins. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion. In pregnancies occurring after the induction of ovulation with gonadotropic preparations, there is an increased risk of miscarriage or abortion, multiple pregnancies, and ectopic pregnancies, congenital malformations.

USE IN PREGNANCY AND LACTATION

Human menopausal gonadotrophin (menotrophins) should not be given during pregnancy or to lactating mothers.

DRUG INTERACTION

Interaction with other medications are unknown. **Gonagen™** can be injected together with hCG when treating infertile males.

OVERDOSE

Aside from possible Ovarian Hyperstimulation Syndrome (OHSS) and multiple gestations, there is no additional information on the consequences of acute overdosage with human menopausal gonadotrophin.

STORAGE

Gonagen™ should be stored in a refrigerator (2 °C to 8 °C temperature). Do not freeze. Keep away from light and wet place. Keep out of reach of children.

PACKAGING

Gonagen™ for injection:

Each box contains 1 vial of Menotrophin BP 75 IU for injection, 1 mL 0.9% NaCl injection in ampoule, 2 mL disposable syringe, alcohol pad, first aid band and ampoule breaker included as accessories.

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Manufactured by

ESKAYEF PHARMACEUTICALS LTD.

RUPGANJ, NARAYANGANJ, BANGLADESH

TM TRADEMARK

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