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Prescribing Information

Menogon

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ampoule with powder contains: Menotropin (human menopausal gonadotropin, HMG) corresponding to 75 IU FSH and 75 IU LH.

PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

CLINICAL PARTICULARS

Therapeutic indications

- Sterility in females with hypo- or normogonadotropic ovarian insufficiency: Stimulation of follicle growth.
- Sterility in males with hypo- or normogonadotropic hypogonadism.

Posology and method of administration

Sterility in females:

The dosage of HMG for the induction of follicle growth in normo- or hypogonadotropic women varies according to the individual. The amount depends on ovarian response and should be checked by ultrasound examinations of the ovaries and measuring estradiol levels. If the HMG dosage is too high for the treated individual, multiple uni- and bilateral follicle growth can occur.

HMG is administered intramuscularly or subcutaneously and in general, the therapy is begun with a daily dosage corresponding to 75–150 IU FSH. If the ovaries do not respond, the dosage can slowly be increased until a rise in estradiol secretion and follicle growth is evident. Treatment with the same dosage of HMG continues until the desired pre-ovulatory estradiol serum level is attained. If the level rises too quickly, the dosage should be reduced. To induce ovulation, 5000 or 10000 IU HCG are injected i.m. 1 to 2 days after the last HMG administration.

Note: After a HMG dosage too high for the corresponding individual has been administered the following HCG administration can cause an unintentional hyperstimulation of the ovaries.

Sterility in males:

Initially, 3 X 1000 to 3000 IU HCG a week are administered until a normal testosterone serum level is reached. Then, an additional dose of HMG (3 X 75–150 IU FSH + 75–150 IU LH) per week is administered i.m. for a few months.

Method of administration

Menogon is administered by intramuscular or subcutaneous injection.

Selection of patients

Women:

1. Before treatment with Menogon is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. This should include a hystero-salpingogram (to rule out uterine and tubal pathology) and documentation of anovulation by means of basal body temperature, serial vaginal smears, examination of cervical mucus, determination of serum (or urine) progesterone, urinary pregnanediol and endometrial biopsy.
2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.
3. Careful examination should be made to rule out the presence of an early pregnancy.
4. Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory disorders. Cervical dilation and curettage should always be done for abnormal uterine bleeding or other signs of endometrial abnormalities.
5. Evaluation of the husband's fertility potential should be included in the workup.

Men:

Patient selection should be made based on a documented lack of pituitary function.

Prior to hormonal therapy, these patients will have low testosterone levels and low or absent gonadotropin levels. Patients with primary hypogonadotropic hypogonadism will have a subnormal development of masculinization, and those with secondary hypogonadotropic hypogonadism will have decreased masculinization.

Contra-indications

In females:

- Pregnancy
- Enlargement of the ovaries or cysts that is not caused by polycystic ovarian syndrome
- Gynecological bleeding whose cause is unknown
- Tumors in the uterus, ovaries and breasts
- Prior hypersensitivity to Menotropins or to any of the excipients
- A high FSH level indicating primary ovarian failure
- The presence of uncontrolled thyroid and adrenal dysfunction
- The presence of any cause of infertility other than anovulation

In males:

- Carcinoma of the prostate
- Testicular tumors
- Normal gonadotropin levels indicating normal pituitary function
- Elevated gonadotropin levels indicating primary testicular failure
- Infertility disorders other than hypogonadotropic hypogonadism

The following conditions should be properly treated before HMG-therapy is begun:

- Dysfunctions of the thyroid gland and cortex of the suprarenal gland
- Hyperprolactinemia
- Tumors in the pituitary or in the hypothalamic glands

Special warnings and special precautions for use

In pregnancies occurring after induction of ovulation with gonadotropic preparations, there is an increased risk of miscarriage, multiplets and ectopic pregnancies.

HCG should not be administered to induce ovulation in females whose ovaries have unintentionally been hyperstimulated.

When treating sterile women, ovarian activity should be checked (ultrasound and estradiol levels in serum) prior to HMG administration. During treatment, these tests should be carried out every one to two days until stimulation occurs.

Ovarian response can also be measured using a cervix index. Close supervision is imperative during treatment. Treatment should be immediately discontinued if unintentional hyperstimulation occurs.

This warning is particularly important with respect to patients with polycystic ovarian disease. The severe form of ovarian hyperstimulation syndrome may be life-threatening and is characterized by large ovarian cysts (prone to rupture), ascites, very often hydrothorax and occasionally thromboembolic phenomena.

Interaction with other medicaments and other forms of interaction

Interaction with other medicaments is unknown.

HMG can be injected together with HCG when treating infertile males.

Pregnancy and lactation

There is no indication for HMG to be used during pregnancy and lactation period.

Effects on ability to drive and use machines

None.

Undesirable effects

Sensitivity to Menogon – febrile reaction which may be accompanied by chills, musculoskeletal aches or pain, malaise and fatigue have occurred after the administration of Menogon. It is not clear whether or not these were pyrogenic responses or possible allergic reactions.

In addition, reports of "flu-like symptoms" including fever, chills, musculoskeletal aches, joint pains, nausea, headache and malaise have been received.
- Gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal cramps, bloating).
- Pain, rash, swelling and/or irritation at the site of injection.
- Body rashes.
- Dizziness, tachycardia, dyspnea, tachypnea.

The following medical events have been reported subsequent to pregnancies resulting from Menogon therapy:
- Ectopic pregnancy.
- Congenital abnormalities.

Treatment with HMG can often lead to ovarian hyperstimulation. This, however, mostly becomes clinically relevant only after HCG has been administered to induce ovulation. This can lead to the formation of large ovarian cysts that tend to rupture and can cause intra-abdominal bleeding as well. In addition, ascites, hydrothorax, oliguria, hypotension, and thromboembolic phenomena can occur. Treatment should be immediately discontinued when the first signs of hyperstimulation can be detected sonographically and physically felt e.g. pain and palpable enlargement in the lower abdomen. With pregnancy, these side effects can intensify, continue over a long period of time, and be life-threatening.

Unintentional multiple pregnancies occur more often during treatment with HMG.

Occasionally, treatment with HMG is accompanied by nausea and vomiting.

In single cases, hypersensitivity reactions and fever can occur during treatment with HMG. The administration of Menogon may lead to reactions at the injection site: reddening, pain, swelling and itching. In very rare cases, long term usage can lead to the formation of antibodies making treatment ineffectual.

Men:

Gynecomastia may occur occasionally during Menogon HCG therapy. This is a known effect of HCG treatment.

Overdose

Treatment with HMG can lead to hyperstimulation of the ovaries. This, however, mostly becomes clinically relevant only after HCG has been administered to induce ovulation (please see Undesirable effects section).

No therapy is necessary when a slight hyperstimulation is present (Level I) accompanied by a slight enlargement of the ovaries (ovary size 5-7 cm), excessive steroid secretion, and abdominal pain. The patient should be informed, however, and carefully watched.

Clinical supervision and symptomatic treatment, and perhaps an intravenous volume replacement in case of high hemoglobin concentration, are necessary if hyperstimulation (Level II) with ovarian cysts (ovary size 8-10 cm) is present, accompanied by abdominal symptoms, nausea, and vomiting.

Hospitalization is imperative when serious hyperstimulation (Level III) with large ovarian cysts (ovary size more than 10 cm) is present accompanied by ascites, hydrothorax, enlarged abdomen, abdominal pain, dyspnea, salt retention, hemoglobin concentration, increased blood viscosity, and platelet aggregation with the danger of thromboembolism.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

HMG directly affects the ovaries and the testes. HMG has gametotrophic and steroidogenic effect.

In the ovaries, the FSH-component in HMG induces an increase in the number of growing follicles and stimulates their development. FSH increases the production of estradiol in the granulose cells by aromatizing androgens that originate in the Theca cells under the influence of the LH-component.

In the testes, FSH induces the transformation of premature to mature Sertoli cells.

It mainly causes the maturation of the seminal canals and development of the spermatozoa. However, a high concentration of androgens within the testes is necessary and can be attained by prior treatment using HCG.

Pharmacokinetic properties

HMG is not effective when taken orally and is injected i.m. or s.c. HMG's biological effectiveness is mainly due to its FSH and LH content. The pharmacokinetics of Menogon following i.m. or s.c. administration were tested product specifically.

The maximum serum level of FSH is reached 6-48 hours after i.m. injection and 6-36 hours after s.c. injection. After that, the serum level decreases by a half-life of 56 hours (i.m.) and 51 hours (s.c.).

Administered HMG is predominantly discharged renally.

Preclinical safety data

Toxic effects caused by HMG are unknown in humans.

There is no evidence of teratogenic, mutagenic and carcinogenic activity of HMG.

Antibodies against HMG can be built up in single cases following repeated cyclical administration of HMG, causing the treatment to be ineffectual.

PHARMACEUTICAL PARTICULARS

List of excipients

Dry substance: lactose monohydrate, sodium hydroxide for pH-adjustment.

Solvent: sodium chloride, dilute hydrochloric acid for pH-adjustment, water for injection.

Incompatibilities

Not known.

Shelf life

3 years.

Special precautions for storage

To be stored protected from light and not above 25°C.

Nature and contents of container

Pack I:
10 glass ampoules of powder.
10 glass ampoules of solvent.
Pack II:
5 glass ampoules of powder.
5 glass ampoules of solvent.

Instructions for use/handling

The powder for solution for injection must be reconstituted with the solvent provided and should be administered immediately.

MANUFACTURER

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