UNOFFICIAL TRANSLATION

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Menogon 75 IU
Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In women:

- anovulation (including polycystic ovary syndrome);
- controlled ovarian hyperstimulation for the purpose of inducting the development of multiple follicles in connnection with assisted reproduction medicine [e.g.: in-vitro fertilisation/embryo transfer (IVF/ET) and intracytoplasmatic sperm injection (ICSI)].

In men:

- insufficient spermatogenesis caused by hypogonadotropic hypogonadism.

4.2 Posology and method of administration

Treatment with Menogon should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

The duration of use depends on the corresponding indication (see section Posology).

Posology

The dosage regimens described in the following apply to both and intramuscular administration.

Women:

and intraindividually, the ovaries react in very different ways to administered gonadotropins. Therefore, producing a universally applicable dosage scheme is not possible. The dosage should thus be adapted individually to the ovaries' response. Menogon can be administered alone or in combination with a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Recommendations on the dosage and duration of treatment depend on the corresponding treatment protocol.

Women with anovulation:
The Menogon therapy should be commenced within the first 7 days of the menstruation cycle. For at least 7 days of treatment, a daily dosage of 75 to 150 IU of Menogon is recommended. In accordance with clinical control (including ultrasound, preferably in combination with measurement of estradiol values), the subsequent treatment of the patient should be individually adapted. The dosage should not be increased after less than 7 days. The recommended dose increment is 37.5 IU per adjustment, and should not exceed 75 IU.The maximum daily dosage should not exceed 225 IU. In case there is no optimal reaction achieved after 4 weeks of treatment, the treatment should be interrupted for this cycle and started again with a higher dosage in a new cycle.

Once an optimal reaction has been achieved, one single injection of 5,000 to 10,000 IU HCG should be administered one day after the last Menogon injection. The patient should have sexual intercourse both on the day of HCG administration and on the following day. Alternatively, an intrauterine insemination can be performed. The patients should be closely followed up for at least 2 weeks following the HCG administration. If an excessive reaction to Menogon is observed, the course of treatment should be stopped, and no HCG should be administered (see section 4.4). The patient should use non-hormonal contraceptives or renounce sexual intercourse until the beginning of the next menstrual bleeding.

Women with controlled ovarian hyperstimulation for development of multiple follicles for assisted reproduction technology (ART):
In a protocol using down-regulation with a GnRH agonist, the Menogon therapy should be commenced about 2 weeks after the beginning of the agonist treatment.

In a protocol using down-regulation with a GnRH antagonist, Menogon therapy should start on day 2 or 3 of the menstrual cycle.
For at least the first 5 days of treatment, a daily dosage of 150 to 225 IU of Menogon is recommended. In accordance with clinical control (including ultrasound, preferably in combination with measurement of estradiol values), the subsequent treatment of the patient should be individually adapted; the increase of dosage should not exceed 150 IU per step. The maximum daily dosage should not exceed 450 IU. In general, the treatment should not exceed 20 days.

Once an optimal reaction has been achieved, one single injection of up to 10,000 IU HCG should be administered to finish the follicular maturation to prepare the oocytes' release. The patients should be closed followed up for at least 2 weeks following the administration of HCG. If an excessive reaction to Menogon is observed, the course of treatment should be stopped, and no HCG should be administered (see section 4.4). The patient should use non-hormonal contraceptives or renounce sexual intercourse until the beginning of the next menstrual bleeding.

Men:
After normalisation of the testosterone level following administration of the appropriate dosage of HCG (e.g. 1,500 to 5,000 IU, 3 times a week) for 4 to 6 months, Menogon can be administered three times a week with a dosage of 75 or 150 IU, in combination with HCG with the recommended dosage of 1500 IU three times a week. The combined treatment should be continued for at least three to four months until an

improvement of spermatogenesis can be seen. In case the patient does not respond after this period, combination therapy might be necessary until spermatogenesis is achieved. Current clinical data show that 18 months of treatment (or even more) can be necessary until spermatogenesis is achieved.

Paediatric population:
There is no relevant use of Menogon in the paediatric population.

Method of administration

Menogon is intended for subcutaneous (S.C.) or intramuscular (I.M.) injection after reconstitution with the solvent provided. Shaking should be avoided. The solution should not be used if it contains particles or if it is not clear.

4.3 Contraindications

- hypersensitivity to Menotropin or to any of the excipients listed in section 6.1.

In women:
- pregnancy,
- ovarian enlargement or cysts that are not caused by a polycystic ovary syndrome,
- vaginal bleeding of unknown cause,
- uterus, ovarian and breast tumors.

In men:
- prostate carcinoma,
- testicular tumors.

In case of dysfunctions of the thyroid gland and the adrenal cortex, in case of hyperprolactinemia and with tumors in the hypophysis or the hypothalamus corresponding treatment has to be performed prior to the beginning of the therapy with HMG.

Menogon may not be used if non-achievement of the therapy aims is predictable.
This applies to women with
- primary ovarian insufficiency
- deformation of the sexual organs, that make pregnancy impossible
- uterine myomas that make pregnancy impossible.

This applies to men with:
- primary testicular insufficiency.

4.4 Special warnings and precautions for use

Menogon is a potent gonadotropic substance that can have mild up to severe side effects. It should only be administered under supervision of medical doctors who are familiar with the problems and treatment of fertility disorders.

Therapies with gonadotropins require a certain expenditure of time from doctors and medical staff as well as appropriate monitoring facilities. A secure and effective use of Menogon requires regular control of the ovarian reaction by use of ultrasound, preferably in combination with measurement of serum estradiol levels. Interindividually, the reaction to the FSH administration can vary and can be very low in some patients. In order to achieve therapy aims, the lowest effective dosage in relation to the aims of treatment should be administered.

The first Menogon injection should be performed under direct medical supervision.

Women:
Prior to the treatment, the couple's infertility is to be diagnosed in an appropriate way and possible contraindications for pregnancy are to be assessed. The patients are to be examined for hypothyreosis, insufficiency of the adrenal cortex, hyperprolactinemia, and hypophysis or hypothalamus tumors and should be treated accordingly.

In patients who undergo stimulation of the follicular growth – in connection with treatment of anovulatory infertility or ART – enlargement of the ovaries or hyperstimulation may occur. These risks can be minimised by adherence to the recommended dosage and administration regimens and through thorough monitoring of the therapy.

The assessment of the follicular development is to be performed by a medical doctor who is experienced in this context.

Ovarian hyperstimulation syndrome (OHSS)
OHSS differs from uncomplicated ovarian enlargement and can manifest with increasing grades of severity. It includes marked enlargement of the ovaries, high levels of sexual hormones and increase of the fluid permeability of the vessels. The latter can lead to fluid accumulation in the peritoneal, pleural and, in rare cases, in the pericardial cavities.

The following symptoms can be observed in severe cases of OHSS: abdominal pain, distended abdomen, excessive ovarian enlargement, increase in weight, dyspnea, oliguria, and gastrointestinal symptoms such as nausea, emesis and diarrhea. The clinical examination may reveal hypovolemia, hemoconcentration, electrolyte balance disorders, ascites, hemoperitoneum, pleural effusion, hydrothorax, acute shortness of breath, and thromboembolism.

Excessive ovarian reaction to the gonadotropin treatment rarely leads to OHSS unless the ovulation is not triggered by HCG administration. It is thus advisable not to administer HCG with ovarian hyperstimulation and to instruct the patient to renounce sexual intercourse or use nonhormonal contraceptives for at least 4 days. OHSS can progress very quickly (between 24 hours and several days) and develop to serious symptoms. Therefore patients should be controlled for a period of at least 2 weeks following the HCG administration.

Adherence to the recommended dosage and administration regimens and thorough monitoring of the therapy can minimise the appearance of ovarian hyperstimulation and multiple pregnancy (see sections 4.2 and 4.8). With ART, aspiration of all follicles prior to ovulation can reduce the risk of hyperstimulation.

OHSS can be more severe and of longer duration in cases of pregnancy. OHSS appears most frequently after completion of hormonal treatment and reaches its peak about 7 to 10 days after treatment. Normally, OHSS recedes spontaneously with the beginning of menstruation.

In cases of severe OHSS, the gonadotropin treatment should be stopped (if this has not been done yet), the patient is to be admitted to hospital, and a special OHSS treatment is to be started.

OHSS appears more frequently in women with polycystic ovarian syndrome (PCO).

...ltiple pregnancy
...ultiple pregnancy, particularly those of higher order, bear an increased risk of maternal and perinatal complications.

In patients who undergo an ovulation induction with Menogon, the risk of multiple pregnancy is higher in relation to natural conception. In order to minimise the risk of multiple pregnancy, thorough monitoring of the ovarian reaction is recommended.

In patients who undergo ART, the risk of multiple pregnancy mainly depends on the number of transferred embryos, their quality and the patient's age.

Prior to the treatment, the patient is to be informed about the potential risk of multiple pregnancy.

Premature birth / miscarriage
Premature birth or miscarriage are seen more frequently in patients who undergo ART or a stimulation of follicular growth for the purpose of causing ovulation than in the average population.

Ectopic pregnancy
In women with a history of tubal diseases, there is a risk of of ectopic pregnancy, no matter if pregnancy has been caused by spontaneous conception or by fertility treatment. A prevalence of 2 to 5% of ectopic pregnancy after IVF has been reported, in relation to 1 to 1.5% in the normal population.

Neoplasms of the reproduction organs
In women who have undergone multiple fertilisation treatment cycles, benign and malign neoplasms of the ovaries and other reproduction organs have been reported.
It is still in question as to whether treatment with gonadotropins increases the basic risk of these tumors in infertile women.

Congenital deformations
The prevalence of congenital deformations following ART can be slightly higher than with spontaneous conception. This can probably be attributed to different parental prior encumbrance (e.g. mother's age, sperm characteristics) and multiple pregnancy.

Thromboembolism
Women with generally recognised risk factors for thromboembolic events, such as personal or family history, severe obesity (Body Mass Index > 30 kg/m^2) 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 gonadotrophin administration need to be weighed against the risks. It should be noted however, that pregnancy itself also carries an increased risk of thromboembolic events.

Men:
Increased endogenous FSH levels indicate a primary testicular disorder. These patients do not respond to Menogon/HCG therapy.

Sperm analyses are to be performed 4 – 6 months after the beginning of treatment to enable assessment of the reaction to the therapy.

The use of Menogon may lead to positive results in doping tests.
The use of Menogon for doping purposes may endanger health.

nogon contains sodium, but less than 1 mmol (23 mg) sodium per dose, i.e. essentially "sodium-free".

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Menogon in human beings.

Although there is no clinical experience it is to be expected that the simultaneous use of Menogon and Clomifencitrate can increase the follicular response. With use of a GnRH agonist for the purpose of hypophyseal desensitisation, a higher dose of Menogon may be required to achieve a sufficient follicular reaction.

4.6 Fertility, pregnancy and lactation

Fertility
Menogon is indicated for use in infertility (see section 4.1).

Pregnancy
Menogon is contraindicated in women who are pregnant (see section 4.3).

Lactation
Menogon is contraindicated in women who are lactating (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, Menogon is unlikely to have influence on the patient's ability to drive and use machines.

4.8 Undesirable effects

The assessment of undesirable effects is based on the following grades of frequency:
Very common (≥1/10)
Common (≥1/100 bis <1/10)
Uncommon (≥1/1,000 bis <1/100)
Rare (≥1/10,000 bis <1/1,000)
Very rare (<1/10,000)

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (<1/10,000)
Gastrointestinal disorders		Nausea, Abdominal pain, emesis			
General disorders and administration site conditions	Reactions* and pain at the site of injection	Flu-like symptoms	Fever		
Immune system disorders					Hypersensitivity
Nervous system disorders		Headache			
Reproductive system and breast disorders		Mild, moderate and severe OHSS			

...ss	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (<1/10,000)
...subcutaneous ...sorders		Rash			

* Reactions at the site of injection have been observed in 55 – 60 % of the participants in clinical studies on local tolerability. In about 12 %, the reaction has been assessed as severe. In most cases, the reaction occurred following subcutaneous administration. After intramuscular administration, reactions at the site of injection have been observed in up to 13 % of the study participants.

Menogon treatment has shown single cases of anaphylactic reactions.

In connection with ovarian hyperstimulation, the use of gonadotropins has shown single cases of thromboembolic complications and ovarian torsions.

Pregnancy commencing subsequent to infertility treatment with gonadotropins such as Menogon can end up in spontaneous abortion more frequently than normal pregnancy.

Men: In connection with treatment with gonadotropins, gynecomastia, acne and increase in weight have been reported.

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 to:

Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn
Website: www.bfarm.de

4.9 Overdose

Treatment with HMG can lead to a hyperstimulation of the ovaries which, however, in most cases becomes clinically relevant only after the administration of HCG for the purpose of triggering ovulation (see section 4.8 Undesirable effects).

With mild hyperstimulation (grade I) with mild ovarian enlargement (ovarian size 5 - 7 cm), with excessive steroid secretion and abdominal problems, no therapy is required. However, the patient is to be informed and thoroughly followed up. With hyperstimulation (grade II) with ovarian cysts (ovarian size 8 - 10 cm), abdominal symptoms, nausea and emesis, clinical monitoring and symptomatic treatment or, if necessary, intravenous volume substitution with higher hemoconcentration is indicated. With severe hyperstimulation (grade III) with large ovarian cysts (ovarian size > 10 cm), ascites, hydrothorax, distended abdomen, abdominal pain, dyspnea, salt retention, hemoconcentration, increased blood viscosity and increased platelet aggregation with the danger of thromboembolism, admission to hospital is inevitable, since life-threatening conditions could arise, making intensive medical measures necessary.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotropins
ATC code: G03GA02

The target organs of the hormonal effect of HMG are the ovaries and testes. HMG has a gametotrophic and steroidogenic effect.

By use of the FSH component, HMG induces an increase of the growing follicles in the ovaries and stimulates their development. FSH increases the production of estradiol in the granulosa cells by aromatising androgens that emerge from the theca cells under influence of the LH component.

In the testicles, FSH induces the transformation from immature to mature Sertoli cells. It mainly has an effect on the maturation of the sperm channels and the development of the spermatozoa. However, a high intratesticular androgen concentration is necessary, which requires previous treatment with HCG.

5.2 Pharmacokinetic properties

HMG is orally ineffective and requires intramuscular or subcutaneous injection. The pharmacokinetics of HMG following intramuscular and subcutaneous application has been examined specifically for each preparation. The maximum serum level of FSH is reached 6 – 48 hours after intramuscular injection and 6 – 36 hours after subcutaneous injection. Subsequently, the serum level decreases with a 56-hour (intramuscular) resp. 51-hour (subcutaneous) half-life.
HMG is mainly excreted renally.

Bioavailability
The bioavailability of Menogon is higher after subcutaneous application than after intramuscular application. The FSH values after intramuscular and subcutaneous application (dosage: 300 IU) were:

intramuscular: AUC_{0-} = 320.1 mIE/ml x h;
c_{max} = 4.15 mIE/ml;
t_{max} = 18 h

subcutaneous: AUC_{0-} = 385.2 mIE/ml x h;
c_{max} = 5.62 mIE/ml;
t_{max} = 12 h

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans, which is not known from the extensive clinical experience.
Reproduction toxicity studies have not been carried out to evaluate the effects of Menogon during pregnancy or post partum as Menogon is not indicated during these periods.
Menogon consist of naturally occurring hormones and should be expected to be non-genotoxic. Carcinogenicity studies have not been carried out as the indication is for short term treatment.
In single cases, formation of antibodies against HMG can occur after repeated cyclic HMG administration, which can cause the treatment to fail.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients

powder:
lactose monohydrate
sodium hydroxide
solvent:
sodium chloride
hydrochloric acid 10 %
water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze. Store in the original container in order to protect from light.

6.5 Nature and contents of container

Menogon is available in the following pack sizes:

OP including 5 ampoules with powder and solvent
OP including 10 ampoules with powder and solvent

6.6 Special precautions for disposal

No particular requirements.

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

7. MARKETING AUTHORISATION HOLDER

FERRING GmbH
Wittland 11
24109 Kiel

Co-distributor
FERRING Arzneimittel GmbH
Fabrikstraße 7
24103 Kiel
tel.: (0431) 58520
fax.: (0431) 585274

MARKETING AUTHORISATION NUMBER

6081027.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

December 21, 2005

10. DATE OF REVISION OF THE TEXT

October 2013

11. PRESCRIPTION/PHARMACY STATUS

Prescription only

For further information please feel free to contact us at the following e-mail address: info-service@ferring.de