SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

MENOGON HP 75 IU
Powder and solvent for solution for injection

2. Qualitative and quantitative composition

Active ingredient: 1 injection bottle with powder contains highly purified menotrophin (human menopausal gonadotrophin, HMG) corresponding to FSH 75 IU and LH 75 IU.

For the full list of excipients see section 6.1.

3. Pharmaceutical form

Powder and solvent for solution for injection

Appearance of powder: white to off-white lyophilisation cake.
Appearance of solvent: clear colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

MENOGON HP is indicated for the treatment of female infertility in the following clinical situations:

- Anovulation [including polycystic ovarian disease (PCOD)] in women who have been unresponsive to treatment with clomiphene citrate.

- Controlled ovarian hyperstimulation to induce the development of multiple follicles for assisted reproductive technologies (ART) [e.g.: in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-Follopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)]

4.2 Posology and method of administration

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

Dosage
Dosage regimens described below are identical for subcutaneous and intramuscular administration.

There are great inter- and intraindividual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme.

The dosage should, therefore, be adjusted individually depending on the ovarian response. MENOGON HP can be given alone or in combination with a gonadotrophin-releasing hormone (GnRH) agonist or antagonist. Recommendations about dosage and duration of treatment may change depending on the actual treatment protocol.

Women with anovulation (including PCOD)
The object of MENOGON HP therapy is to develop a single Graafian follicle from which the oocyte will be liberated after the administration of hCG.

MENOGON HP therapy should start within the initial 7 days of the menstrual cycle. The recommended initial dose of MENOGON HP 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 oestradiol 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 recommence 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 MENOGON HP injection. The patient is recommended to have coitus on the day of and the day following hCG administration. Alternatively intrauterine insemination (IUI) may be performed. If an excessive response to MENOGON HP is obtained, treatment should be stopped and hCG withheld (see section 4.4) and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started.

Women undergoing controlled ovarian hyperstimulation for multiple follicular development for assisted reproductive technologies (ART)
In a protocol using downregulation with a GnRH agonist, MENOGON HP therapy should start approximately 2 weeks after the start of agonist treatment.

In a protocol using downregulation with a GnRH antagonist, MENOGON HP therapy should start on day 2 or 3 of the menstrual cycle.
The recommended initial dose of MENOGON HP 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 oestradiol 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 MENOGON HP is obtained, treatment should be stopped and hCG withheld (see section 4.4) and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started.

Paediatric population
There is no relevant use of MENOGON HP in the paediatric population.

Method of administration
MENOGON HP is intended for subcutaneous (S.C.) or intramuscular (I.M.) injection after reconstitution with the solvent provided. The powder should be reconstituted immediately prior to use. In order to avoid the injection of large volumes up to 3 vials of MENOGON HP may be dissolved in 1 ml of 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

MENOGON HP is contraindicated in women who have:
- Tumours of the pituitary gland or hypothalamus
- Ovarian, uterine or mammary carcinoma
- Pregnancy and lactation
- Gynaecological haemorrhage of unknown aetiology
- Hypersensitivity to the active substance or any of the excipients listed in section 6.1
- Ovarian cysts or enlarged ovaries not due to polycystic ovarian disease

In the following situations treatment outcome is unlikely to be favourable, and therefore MENOGON HP should not be administered:
- Primary ovarian failure
- Malformation of sexual organs incompatible with pregnancy
- Fibroid tumours of the uterus incompatible with pregnancy

4.4 Special warnings and precautions for use

MENOGON HP is a potent gonadotrophic substance capable of causing mild to severe adverse reactions, and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonadotrophin therapy requires a certain time commitment by physicians and supportive health professionals, and calls for monitoring of ovarian response with ultrasound, alone or in combination with measurement of serum oestradiol levels, on a regular basis. There is considerable inter-patient variability in response to menotrophin administration, with a poor response to menotrophin in some patients. The lowest effective dose in relation to the treatment objective should be used.

The first injection of MENOGON HP should be performed under direct medical supervision.

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinaemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.

Patients undergoing stimulation of follicular growth, whether in the frame of a treatment for anovulatory infertility or ART procedures may experience ovarian enlargement or develop hyperstimulation. Adherence to recommended MENOGON HP dosage and regimen of administration, and careful monitoring of therapy will minimise the incidence of such events. Acute interpretation of the indices of follicular maturation requires a physician who is experienced in the interpretation of the relevant tests.

Ovarian hyperstimulation syndrome (OHSS)
OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS is a syndrome that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular

permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

The following symptoms may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events.

Excessive ovarian response to gonadotrophin treatment seldom gives rise to OHSS unless hCG is administered to trigger ovulation. Therefore in cases of ovarian hyperstimulation it is prudent to withhold hCG and advise the patient to refrain from coitus or to use barrier methods for at least 4 days. OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event, therefore patients should be followed for at least two weeks after the hCG administration.

Adherence to recommended MENOGON HP dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy (see sections 4.2 and 4.8). In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation.

OHSS may be more severe and more protracted if pregnancy occurs. Most often, OHSS occurs after hormonal treatment has been discontinued and reaches its maximum severity at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses.

If severe OHSS occurs, gonadotrophin treatment should be stopped if still ongoing, the patient hospitalised and specific therapy for OHSS started.

This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

Multiple pregnancy
Multiple pregnancy, especially high order, carries an increased risk of adverse maternal and perinatal outcomes.

The incidence of multiple pregnancy is increased compared to normal conception in patients who undergo ovulation induction with gonadotrophins. The majority of multiple conceptions are twins. To minimise the risk of multiple pregnancy, careful monitoring of ovarian response is recommended.

In patients undergoing ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the age of the patient.

The patient should be advised of the potential risk of multiple births before starting treatment.

Pregnancy wastage
The incidence of pregnancy wastage by miscarriage or abortions is higher in patients undergoing stimulation of follicular growth for ART procedures than in the normal population.

Ectopic pregnancy
Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatment. The

prevalence of ectopic pregnancy after IVF has been reported to be 2 to 5%, as compared to 1 to 1.5% in the general population.

Reproductive system neoplasms
There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment.
It is not yet established if treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.

Congenital malformation
The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and multiple pregnancies.

Thromboembolic events
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.

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

MENOGON HP contains sodium, but less than 1 mmol (23 mg) sodium per dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No drug/drug interaction studies have been conducted with MENOGON HP in humans.

Although there is no controlled clinical experience, it is expected that the concomitant use of MENOGON HP and clomiphene citrate may enhance the follicular maturation. When using GnRH agonist for pituitary desensitisation, a higher dose of MENOGON HP may be necessary to achieve adequate follicular maturation.

4.6 Fertility, pregnancy and lactation

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

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

Lactation
MENOGON HP 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 HP is unlikely to have influence on the patient's ability to drive and use machines.

4.8 Undesirable effects

The most frequently reported adverse drug reactions reported during treatment with MENOGON HP in clinical trials are Ovarian hyperstimulation syndrome (OHSS) abdominal pain, headache, abdominal distension, injection site reactions, with an incidence rate up to 5 %. The table below displays the main adverse drug reactions in women treated with MENOGON HP in clinical trials distributed by system organ classes and frequency. Further, the ADRs seen during post-marketing experience are mentioned with unknown frequency.

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Not known (cannot be estimated from the available data)**
Eye disorders				Visual disorders [a]
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea	Emesis, abdominal discomfort, diarrhoea		
General disorders and administration site conditions	Injection site reactions [b]	Fatigue		Pyrexia, Malaise
Immune system disorders				Hypersensitivity reactions [c]
Investigations				Weight increased
Musculoskeletal and connective tissue disorders				Musculoskeletal pain [d]
Nervous system disorders	Headache	Dizziness		
Reproductive system and breast disorders	OHSS [e], pelvic pain [f]	Ovarian cyst, breast complaints [g]		Ovarian torsion [e]
Skin and subcutaneous tissue disorders			Acne, rash	Pruritus, urticaria
Vascular disorders		Hot flushes		Thromboembolism [e]

[a] Individual cases of temporary amaurosis, diplopia, mydiasis, scotoma, photopsia, vitreous floaters, vision blurred and vision impairment have been reported as visual disorders during the post-marketing period.

[b] Most frequently reported injection site reaction was injection site pain.

[c] Cases of localised or generalised allergic reactions, including anaphylactic reaction, along with associated symptomatology have been reported rarely.

[d] Musculoskeletal pain includes arthralgia, back pain, neck pain and pain in extremities.

[e] Gastrointestinal symptoms associated with OHSS such as abdominal distension and discomfort, nausea, vomiting and diarrhoea have been reported with MENOGON HP in clinical trials. In cases of severe OHSS ascites and pelvic fluid collection, pleural effusion, dyspnoea, oliguria, thromboembolic events and ovarian torsion have been reported as rare complications.

[f] Pelvic pain includes ovarian pain and adnexa uteri pain.

[g] Breast complaints include breast pain, breast tenderness, breast discomfort, nipple pain and breast swelling.

Unwanted multiple pregnancy is more common during treatment with HMG.

Pregnancies which result from infertility treatment with gonadotrophins such as Menogon HP may end more frequently in spontaneous abortions than normal pregnancies.

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

The effects of an overdose are unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophins
ATC code: G03G A02

MENOGON HP contains menotrophin (hMG) which is composed of follicle stimulating hormone (FSH) and luteinising hormone (LH). In addition, Human Chorionic Gonadotrophin (hCG), a hormone occurring in postmenopausal urine, is present in MENOGON HP and contributes to the LH activity.

Menotrophin, 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 primary ovarian failure. FSH is the primary driver of follicular recruitment and growth in early folliculogenesis, while LH is important for ovarian steroidogenesis and

pre-ovulatory follicular maturation. Follicular growth can be stimulated by FSH in the total absence of LH (e.g. in hypogonadotrophic hypogonadism), but the resulting follicles develop abnormally and are associated with low oestradiol levels and an insufficient follicular maturation may occur.

In line with the action of LH activity in enhancing stereoidogenesis, oestradiol levels associated with treatment with MENOGON HP are higher than with recombinant FSH preparations in downregulated IVF/ICSI cycles. This issue should be considered when monitoring patients' response based on oestradiol levels. The difference in oestradiol levels is not found when using low-dose ovulation induction protocols in anovulatory patients.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of the FSH in MENOGON HP has been documented. After 7 days of repeated dosing with 150 IU MENOGON HP in downregulated healthy female volunteers, maximum plasma FSH concentrations (baseline-corrected) (mean ± SD) were 8.9 ± 3.5 IU/L and 8.5 ± 3.2 IU/L for the subcutaneous and intramuscular administration, respectively. Maximum FSH concentrations were reached within 7 hours for both routes of administration. After repeated administration, FSH was eliminated with a half-life (mean ± SD) of 30 ± 11 hours and 27 ± 9 hours for the subcutaneous and intramuscular administration, respectively. Although the individual LH concentration versus time curves show an increase in the LH concentration after dosing with MENOGON HP, the data available were too sparse to be subjected to a pharmacokinetic analysis.

Menotrophin is excreted primarily via the kidneys.

The pharmacokinetics of MENOGON HP in patients with renal or hepatic impairment has not been investigated.

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 HPduring pregnancy or post partum as MENOGON HP is not indicated during these periods.
MENOGON HP 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.

6. Pharmaceutical particulars

6.1 List of excipients

Powder:
Lactose monohydrate
Polysorbate 20
Sodium hydroxide
Hydrochloric acid 36 %

Solvent:

Sodium chloride
Hydrochloric acid 10%
Water for injection

6.2 Incompatibilities

MENOGON HP should not be administered in the same injection with other products, except Ferring's urofollitrophin Bravelle 75 IU. Studies have shown that co-administration of MENOGON HP and urofollitrophin does not significantly alter the expected bioavailability.

6.3 Shelf life

2 years

For immediate use following reconstitution.

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

Powder: 2 ml colourless glass (type I) injection bottle with rubber stopper closed with a cap

Solvent: 1 ml colourless glass (type I) ampoule

MENOGON HP is available in the following pack sizes:

OP with each 5 injection bottles with powder and
5 ampoules with solvent,
5 syringes with cannulas to dissolve the powder in the solvent,
5 injection needles,
5 single-use alcohol swabs

OP with each 10 injection bottles with powder and
10 ampoules with solvent,
10 syringes with cannulas to dissolve the powder in the solvent,
10 injection needles,
10 single-use alcohol swabs

6.6. Special precautions for disposal and other instructions for handling

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

7. Marketing authorisation holder

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24109 Kiel

Codistributor
FERRING Arzneimittel GmbH
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8. Marketing authorisation number

07144/08090/REN/2021

9. Date of first authorisation/renewal of the authorisation

Feb 21, 2022

10. Date of revision of the text

June 2015

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