MENOPUR®

FERRING

Name of the medicinal product
MENOPUR

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.

Pharmaceutical form
Powder and solvent for solution for injection

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

Clinical Particulars
Therapeutic Indications
MENOPUR 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)]
•In men, in conjunction with hCG (human chorionic Gonadotropin), by stimulating the development of mature male reproductive cells.

Posology and method of administration
Method of administration
MENOPUR 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. Up to 3 injection bottles of MENOPUR may be dissolved in 1 ml of the solvent provided. The solution should not be used if it contains particles or if it is not clear.

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. MENOPUR 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.
Men:
First, administer 1,000 to 3,000 IU of hCG (human Chorionic Gonadotropin) 3 times weekly until the testosterone level in the blood is normal. Then, administer 75 to 150 IU of Menopur® 3 times weekly for few months.
Menopur® may be injected concomitantly with hCG (human Chorionic Gonadotropin) to treat infertility.
Women with anovulation (including PCOD)
The objective of MENOPUR therapy is to develop a single Graafian follicle from which the oocyte will be liberated after the administration of hCG.

MENOPUR therapy should start within the initial 7 days of the menstrual cycle. The recommended initial dose of MENOPUR 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 MENOPUR 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 MENOPUR is obtained, treatment should be stopped and hCG withheld 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 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 MENOPUR dosage, regimen of administration and careful monitoring of therapy will minimize the incidence of ovarian hyperstimulation and multiple pregnancy. 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.

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 minimize 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/m2) 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 MENOPUR may lead to positive results in doping tests.
The use of MENOPUR for doping purposes may endanger health.

Interaction with other medicinal products and other forms of interaction

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

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

Pregnancy & lactation.
MENOPUR is contraindicated in women who are pregnant or lactating
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, MENOPUR is unlikely to have influence on the patient's ability to drive and use machines.

Example protocol for MENOPUR treatment with GnRH agonists:
In line with clinical trials that involved down regulation with GnRH agonists, MENOPUR therapy should start approximately 2 weeks after the start of agonist treatment. The recommended initial dose of MENOPUR 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.
In protocols not involving downregulation, MENOPUR therapy should start on day 2 or 3 of the menstrual cycle. It is recommended to use the dose ranges and regimen of administration suggested above for protocols with down regulation with GnRH agonists.
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 MENOPUR is obtained, treatment should be stopped and hCG withheld and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started.

Contraindications
MENOPUR 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 used in the formulation
- Ovarian cysts or enlarged ovaries not due to polycystic ovarian disease

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

MENOPUR is contraindicated in men in cases of Prostate cancer & Testicular tumours

Special warnings and precautions for use
MENOPUR 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 MENOPUR 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 MENOPUR dosage and regimen of administration, and careful monitoring of therapy will minimize 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

The most frequently reported adverse drug reactions reported during treatment with MENOPUR in clinical trials are abdominal pain, headache, injection site reactions and injection site pain, with an incidence rate up to 10%.
Common (≥ 1/100 to < 1/10):
Gastrointestinal disorders: Abdominal pain, nausea, enlarged abdomen
General disorders and administration site conditions: Injection site reaction and pain
Nervous system disorders: Headache

Reproductive system and breast disorders: OHSS, Pelvic pain

Gastrointestinal symptoms associated with OHSS such as abdominal distension and discomfort, nausea, vomiting and diarrhoea have been reported with MENOPUR in clinical trials. As rare complications of OHSS, venous thromboembolic events and ovarian torsion might occur.

Very rare cases of allergic skin reactions, localised or generalised, including anaphylactic reaction, have been reported after injection of MENOPUR .

Unwanted multiple pregnancy is more common during treatment with HMG.

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

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

Pharmaceuticals particulars
List of excipients
Powder:
Lactose monohydrate
Polysorbate 20
Sodium hydroxide
Hydrochloric acid 36 %

Solvent:
Sodium chloride
Hydrochloric acid 10%
Water for injection

Incompatibilities
MENOPUR 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 MENOPUR and urofollitrophin does not significantly alter the expected bioavailability.

Shelf life
See outer carton
For immediate use following reconstitution .

Special precautions for storage
Store protected from light and below + 30 °c.

Nature and contents of container
Powder:
2ml colourless glass (type I) injection bottle with rubber stopper closed with a cap

Solvent:
1ml colourless glass (type I) ampoule

Content of container:
- 5 vials powder + 5 ampoules solvent
-10 vials powder + 10 ampoules solvent

Special precautions for disposal and other instructions for handling
Any unused product or waste material should be disposed in accordance with local requirements.

Manufacturer & Marketing Authorization Holder:
Ferring GmbH
Wittland 11, DE-24109 Kiel,
Germany

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THIS IS A MEDICINE
- A MEDICINE IS A PRODUCT WHICH AFFECTS YOUR HEALTH. AND ITS CONSUMPTION CONTRARY TO INSTRUCTIONS IS DANGEROUS FOR YOU.
- STRICTLY FOLLOW THE DOCTOR'S PRESCRIPTION, THE METHOD OF USE AND THE INSTRUCTIONS OF THE PHARMASIST WHO SOLD THE MEDICINE.
- THE DOCTORS AND THE PHARMACIST ARE EXPERTS IN MEDICINE, ITS BENEFITS AND RISKS.
- DO NOT BY YOURSELF INTERRUPT THE PERIOD OR TREATMENT PRESCRIBED FOR YOU.
- DO NOT REPEAT THE SAME PRESCRIPTION WITHOUT CONSULTING YOUR DOCTOR.
-KEEP THE MEDICINE OUT OF REACH OF CHILDREN.

Council of Arab Health Ministers
Union of Arab Pharmacists

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