

MENOPUR®

Description of the Medicinal Product

MENOPUR, powder and solvent for solution for injection, 75 IU

Active ingredient: Menotrophin HP

Qualitative and Quantitative Composition

Each vial with powder contains highly purified menotrophin (human menopausal gonadotrophin, HMG) corresponding to follicle stimulating hormone activity FSH 75 IU and luteinising hormone activity LH 75 IU.

Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in post-menopausal urine, is present in MENOPUR and is the main contributor of the LH activity.

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 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 hyper-stimulation to induce the development of multiple follicles for assisted reproductive technologies (ART) (e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intra-cytoplasmic sperm injection (ICSI)).

Dosage and Method of Administration

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

MENOPUR is intended for subcutaneous (S.C.) or intramuscular (I.M.) injection after reconstitution with the solvent provided. Vigorous shaking should be avoided. The powder should be reconstituted immediately prior to use. In order to avoid the injection of large volumes up to 3 vials of the powder 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 (see Instructions for Use and Handling section).

Dosage

Dosage regimens described below are identical for S.C. and I.M. administration.

There are great inter-individual 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.

Women with anovulation (including PCOD):

The object of MENOPUR therapy is to develop a single Graafian follicle from which the oocyte will be liberated after the administration of human chorionic gonadotrophin (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 clinical monitoring (including ovarian ultrasound alone or in combination with measurement of oestradiol levels) subsequent dosing 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. 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 response 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) maybe performed. If an excessive response to MENOPUR is obtained treatment should be stopped and hCG withheld (see Special Warnings and Precautions for Use section) 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 hyper-stimulation for multiple follicular development for assisted reproductive technologies (ART):

In line with clinical trials with MENOPUR that involved downregulation 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 clinical monitoring (including ovarian ultrasound alone or in combination with measurement of oestradiol levels) subsequent dosing 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 with GnRH agonists, 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 downregulation with GnRH agonists.

When a suitable number of follicles have reached an appropriate size a single injection of up to 10,000 IU hCG should be administered to induce final 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 (see Special Warnings and Precautions for Use section) 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

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.

The active ingredient of this drug product is manufactured from human urine. Although the risk is theoretical, and no case of transmission of an infectious agent linked to the use of urine-derived gonadotrophins has been identified, the risk of transmitting infectious agents cannot be completely excluded. There are, however, measures in place to reduce the risk of infections resulting from urine-derived gonadotrophins, including careful selection of urine donors, testing for viral absence in the product and the inclusion of manufacturing steps effective for the inactivation/removal of infectious agents.

Gonadotrophin therapy requires a certain time commitment by physicians and supportive healthcare 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 hyper-stimulation. Adherence to recommended MENOPUR dosage and regimen of administration and careful monitoring of therapy will minimise the incidence of such events. Acute interpretation of the indices of follicle development and maturation requires a physician who is experienced in the interpretation of the relevant tests.

Ovarian Hyper-stimulation 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 hyper-stimulation 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 minimise the incidence of ovarian hyper-stimulation and multiple pregnancy (see Dosage and method of administration and Undesirable Effects sections). In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyper-stimulation.

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 peri-natal outcomes.

In patients undergoing ovulation induction with gonadotrophins, the incidence of multiple pregnancies is increased compared with natural conception. 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 abortion 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.

Interaction with Other Medicinal Products and Other Forms of Interaction

No medicine/medicine 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 response. When using GnRH agonists for pituitary desensitisation, a higher dose of MENOPUR may be necessary to achieve adequate follicular response.

Pregnancy and lactation

MENOPUR is contraindicated in women who are pregnant or lactating.

To date there are no signs of risk of teratogenicity when gonadotrophins are used clinically for ovarian hyper-stimulation. Data on exposed pregnancies are insufficient. Animal experiments did not reveal teratogenic effects.

Effects on Ability to Drive and Use Machinery

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.

Undesirable Effects

The most frequently reported adverse medicine 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%. The table below displays the main adverse medicine reactions in women treated with MENOPUR in clinical trials distributed by system organ classes (SOCs) and frequency.

System Organ Class	Common (> 1/100 and < 1/10)
Gastrointestinal disorders	Abdominal pain, nausea, enlarged abdomen
General disorders and administration site condition	Injection site reaction, Injection site pain
Nervous system disorders	Headache
Reproductive system 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 reactions, localised or generalised, including anaphylactic reaction, have been reported after injection of MENOPUR.

Overdose

The effects of an overdose is unknown, nevertheless one could expect ovarian hyper-stimulation syndrome to occur.

Pharmacological Properties

Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophins

ATC code: G03G A02

Human Chorionic Gonadotrophin (HCG), a naturally occurring hormone in post-menopausal urine, is present in MENOPUR and is the main contributor of 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 is involved in the physiological events leading to the development of a competent pre-ovulatory follicle. Follicular growth can be stimulated by FSH in the total absence of LH, but the resulting follicles develop abnormally and are associated with low oestradiol levels and inability to luteinise to a normal ovulatory stimulus.

In line with the action of LH activity in enhancing steroidogenesis, oestradiol levels associated with treatment with MENOPUR 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.

Pharmacokinetic properties

The pharmacokinetic profile of the FSH in MENOPUR has been documented. After 7 days of repeated dosing with 150 IU MENOPUR in downregulated healthy female volunteers, maximum plasma FSH concentrations (baseline-corrected) (mean \pm SD) were 8.9 ± 3.5 IU/L

and 8.5 ± 3.2 IU/L for the SC and IM 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 \pm SD) of 30 ± 11 hours and 27 ± 9 hours for the SC and IM administration, respectively. Although the individual LH concentration versus time curves show an increase in the LH concentration after dosing with MENOPUR, the data available were too sparse to be subjected to a pharmacokinetic analysis.

Menotrophin is excreted primarily via the kidneys.

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

Preclinical safety data

Given the extensive clinical experience with menotrophin, there have been limited preclinical safety studies with MENOPUR.

Pharmaceutical Particulars

List of Excipients

Powder: lactose monohydrate, polysorbate 20, sodium hydroxide, hydrochloric acid

Solvent: sodium chloride, hydrochloric acid, water for injections.

Incompatibilities

MENOPUR should not be administered in the same injection with other products.

Special Precautions for Storage

Do not store above 25°C. Do not freeze. Store in the original container.

Nature and Contents of Container

MENOPUR is available in the following containers and pack sizes:

Powder: 2 ml colourless glass (Type I) vials with rubber stopper closed with a cap.

Solvent: 1 ml colourless glass (Type I) ampoule.

The product is supplied in packs of 5 or 10 vials with the corresponding number of solvent ampoules.

Instructions for Use and Handling

The powder should only be reconstituted with the solvent provided in the package.

Attach the reconstitution needle to the syringe. Withdraw the entire contents from the ampoule with solvent and inject the total contents into the vial containing the powder. The powder should dissolve quickly to a clear solution. If not, roll the vial gently between the hands until the solution is clear. Vigorous shaking should be avoided.

If needed, the solution can be drawn up into the syringe again to transfer it to the next vial with powder until the prescribed dose has been reached. Up to three powder vials can be dissolved with one ampoule of solvent.

When the prescribed dose has been reached, draw up the mixed solution from the vial into the syringe, change to the hypodermic needle and administer immediately.

The reconstituted solution should not be administered if it contains particles or is not clear.

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

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