Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

MENOPUR® 75IU

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial with powder for solution for injection contains: highly purified Menotrophin (human menopausal gonadotrophin, hMG) corresponding to 75 IU FSH and 75 IU LH.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Sterility in females with hypo or normogonadotropic ovarian insufficiency: stimulation of follicle growth.
- Sterility in males with hypo or normogonadotropic hypogonadism: In combination with hCG to stimulate spermatogenesis.

4.2 Posology and method of administration

Posology: single and daily dosages

Sterility in females.

The dosage of hMG for the induction of follicle growth in normo- or hypogonadotropic woman varies according to the individual. The amount depends on ovarian reaction 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 pre-ovulatory estradiol serum level is attained. If the level rises too quickly, the dosage should be reduced. To induce ovulation, 5,000 or 10,000 IU hCG are injected IM to 2 days after the last hMG administration.

Note: after a hMG dosage too high for corresponding individual has been administered, the following hCG administration can cause an unintentional hyperstimulation of the ovaries.

Sterility in males.

Initially, 3 x 1,000 to 3,000 hCG a week are administered until a normal testosterone serum level is reached.

Children:

Not recommended for use in children.

Elderly:

Not recommended for use in the elderly.

Then, an additional dose of hMG (3 x 75 to 150 IU FSH + 75 to 150 IU LH) per week is administered IM for a few months.

Method of Administration:

Menopur® is administered by intramuscular or subcutaneous injection.

4.3 Contraindications

Men and Women

MENOPUR is contraindicated in men and women with:

- Tumours of the pituitary gland or hypothalamus
- Hypersensitivity to the active substance or any of the excipients used in the formulation (see section 6.1)

Men

- Tumours in the testes
- Prostate carcinoma

Women

- Ovarian, uterine or mammary carcinoma
- Pregnancy and lactation
- Gynaecological haemorrhage of unknown aetiology
- 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
- Structural abnormalities in which a satisfactory outcome cannot be expected, for example, tubal occlusion (unless superovulation is to be induced for IVF), ovarian dysgenesis, absent uterus or premature menopause

4.4 Special warnings and precautions for use

MENOPUR is a potent gonadotropic 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, hyperprolactinemia 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 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 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 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.

If urinary oestrogen levels exceed 540 nmol (150 micrograms)/24 hours, or if plasma 17 beta-oestradiol levels exceed 3000 pmol/L (800 picograms/ml), or if there is any steep rise in values, there is an increased risk of hyperstimulation and MENOPUR treatment should be immediately discontinued and human chorionic gonadotrophin withheld. Ultrasound will reveal any excessive follicular development and unintentional hyperstimulation.

The severe form OHSS may be life-threatening and is characterized by large ovarian cysts (prone to rupture), acute abdominal pain, ascites, very often hydrothorax and occasionally thromboembolic phenomena. Other symptoms that may be observed include: 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, haemoperitoneum, pleural effusions and acute pulmonary distress.

Excessive ovarian response to gonadotrophin treatment seldom gives rise to OHSS unless hCG is administered to trigger ovulation. Therefore, in cases of ovarian hyperstimulation, the patient should refrain from coitus or to use barrier contraception 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.

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Adherence to recommended MENOPUR 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). Patients undergoing superovulation may be at an increased risk of developing hyperstimulation in view of the excessive oestrogen response and multiple follicular development. 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 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.

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 tumors 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 recognized risk factors for thromboembolic events, such as personal or family history, severe obesity (Body Mass Index > 30kg/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.

4.5 Interactions with other medicinal products and other forms of interaction

No interaction studies have been performed 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 agonist for pituitary desensitization, a higher dose of MENOPUR may be necessary to achieve adequate follicular response.

4.6 Fertility, pregnancy and lactation

Fertility

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

Pregnancy

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

There are no or limited amount of data from the use of menotrophins in pregnant women. No animal studies have been carried out to evaluate the effects of MENOPUR during pregnancy (see section 5.3).

Breast-feeding

MENOPUR is contraindicated in women who are breast-feeding (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, MENOPUR 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 (ADR) during treatment with MENOPUR in clinical trials are Ovarian Hyperstimulation Syndrome (OHSS), abdominal pain, headache, abdominal distension, and injection site pain.

None of these ADRs have been reported with an incidence rate of more than 5%.The table below displays the main ADR in women treated with MENOPUR in clinical trials distributed by system organ classes (SOCs) and frequency. 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)	Unknown
Eye disorders				Visual disorders
Gastrointestinal disorders	Abdominal pain, Abdominal distension, Nausea	Vomiting, Abdominal discomfort, Diarrhoea		
General disorders and administration site condition	Injection site reactions [a]	Fatigue		
Immune system disorders				Hypersensitivity reactions [b]
Investigations				
Musculoskeletal & connective tissue disorders				Musculoskeletal pain [c]
Nervous system disorders	Headache	Dizziness		
Reproductive system	OHSS [d], Pelvic	Ovarian cyst, Breast		Ovarian torsion [d]

disorders	pain[e]	complaints [f]		
Skin and subcutaneous tissue disorders			Acne, Rash	Pruritus, Urticaria
Vascular Disorders		Hot flush		

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

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

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

[d] Gastrointestinal symptoms associated with OHSS such as abdominal distension and discomfort, nausea, vomiting, diarrhoea have been reported with MENOPUR 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.

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

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

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 the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

The effects of an overdose is unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophins

ATC code: G03G A02

Menotrophin (Human Menopausal Gonadotrophin, HMG) is a gonadotrophin extracted from the urine of postmenopausal women It has both luteinising hormone and follicle stimulating hormone activity in a 1:1 ratio. Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in postmenopausal urine, is present in MENOPUR and is the main contributor of the LH activity.

Menotrophin (Human Menopausal Gonadotrophin, HMG) directly affects the ovaries and the testes. hMG has a gametropic 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 oestradiol in the granulosa cells by aromatising androgens that originate in the Theca cells under the influence of the LH-component.

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 luteinize 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 patient's response based on oestradiol levels.

In the testes, FSH induces the transformation of premature to mature Sertoli cells. It mainly causes the maturation of the seminal canals and the development of the spermatozoa. However, a high concentration of androgens within the testes is necessary and can be attained by a prior treatment using hCG.

5.2 Pharmacokinetic properties.

The pharmacokinetics of menotrophin following intramuscular or subcutaneous administration shows great interindividual variability. After 7 days of repeated dosing with 150 IU MENOPUR in downregulated healthy female volunteers, plasma FSH concentrations Cmax (baseline-corrected) (mean ± SD) were 8.9 ± 3.5 IU/L and 8.4 ± 3.2 IU/L for the SC and IM administration, respectively. The area under the curve (AUC_τ) of FSH concentration was (mean ± SD) 180 ± 77 h.IU/L and 166 ± 67 h.IU/L for SC and IM administration, respectively. Maximum FSH concentrations were reached (Tmax) within 7 hours for both routes of administration. After repeated administration, FSH was eliminated with a half-life (T1/2) (mean ± 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.

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 MENOPUR during pregnancy or post-partum as MENOPUR is not indicated during these periods.

MENOPUR 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.

4. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients.

Powder for solution for injection: lactose monohydrate, polysorbate 20, sodium hydroxide and hydrochloric acid for pH-adjustment.

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

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life.

The expiry date of the product is indicated on the packaging materials The reconstituted product should be used immediately and any remaining solution should be discarded.

For immediate and single use following reconstitution

6.4 Storage Conditions

To be stored below 25^0C.

6.5 Nature and Contents of Container

Powder: 2 ml colourless glass (Type I) vial 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.

6.6 Instructions for Use/Handling

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

Attach the reconstitution needle to the syringe. Withdraw the entire content 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. 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.

7 MARKETING AUTHORISATION HOLDER:

Ferring GmbH Kiel, Germany

8. LICENSE HOLDER

Ferring Pharmaceuticals Ltd.
Hashita Street, Industrial Park, Caesarea 3088900

9. MARKETING AUTHORISATION NUMBER(S)

123 86 30045

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