1. NAME OF THE MEDICINAL PRODUCT

MENOPUR multidose 600 IU
MENOPUR multidose 1200 IU

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MENOPUR 600 IU: Each vial of powder contains highly purified menotrophin (human menopausal gonadotrophin, HMG) corresponding to 600 IU human follicle stimulating hormone (FSH) and 600 IU human luteinizing hormone (LH) activity.
MENOPUR 1200 IU: Each vial of powder contains highly purified menotrophin (human menopausal gonadotrophin, HMG) corresponding to 1200 IU follicle stimulating hormone (FSH) and 1200 IU human luteinizing hormone (LH) activity.
Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in postmenopausal urine, is present in MENOPUR and contributes to the overall luteinizing hormone activity. Menotrophin is produced from human urine.
For a 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 lyophilised cake.
Appearance of solvent: clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of 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 spermatogenesis.

4.2 Posology and method of administration

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

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 prior to use. The reconstituted solution is for multiple injections and can be used for up to 28 days. Vigorous shaking should be avoided. The solution should not be used if it contains particles or if it is not clear.

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) may be performed. If an excessive response to MENOPUR 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 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 agonist, 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 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.

Renal/hepatic impairment

Patients with renal and hepatic impairment have not been included in clinical trials (see section 5.2).

4.3 Contraindications

MENOPUR is contraindicated in women and men with:

- Tumours of the pituitary gland or hypothalamus
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

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 administrated:
  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.

Men

- Tumours in the testes
- Prostate carcinoma

4.4 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 preferably 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 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.

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 characterised 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 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 hyperstimulation and multiple pregnancy (see sections 4.2 and 4.8). Patients undergoing controlled ovarian hyperstimulation 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 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.
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 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.

4.5 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 response. When using GnRH agonist for pituitary desensitisation, 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 reactions 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 ADRs 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 and < 1/10)**	**Uncommon (> 1/1000 and < 1/100)**	**Rare (> 1/10000 and < 1/1000)**	**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]
Musculoskeletal & connective tissue disorders				Musculoskeletal pain [c]
Nervous system disorders	Headache	Dizziness		
Reproductive system disorders	OHSS [d], pelvic pain [e]	Ovarian cyst, Breast complaints [f]		Ovarian torsion [d]
Skin and			Acne,	Pruritus,

subcutaneous tissue disorders			Rash	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 and 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 suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported 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 post menopausal 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 (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 stereoidogenesis, 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, maximum plasma FSH concentrations (baseline-corrected) (mean ± SD) were 8.9 ± 3.5 IU/L and 8.5 ± 3.2 IU/L for the SC and IM administration, respectively. The area under the curve (AUC_T) 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 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Lactose monohydrate, polysorbate 20, sodium phosphate dibasic heptahydrate (for pH adjustment), phosphoric acid (concentrated) (for pH adjustment).

Solvent:

Metacresol, 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 After reconstitution, the solution may be stored for a maximum of 28 days at not more than-25°C. Do not freeze.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original package in order to protect from light.

For storage condition of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

MENOPUR 600 IU:

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

Solvent: 1 ml pre-filled syringe (type I glass) with rubber (type I) tip cap and plunger rubber stopper .

Each pack contains 1 vial of powder, 1 pre-filled syringe with solvent for reconstitution, 1 needle for reconstitution and 9 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles.

MENOPUR 1200 IU:
Powder: 2 ml colourless glass (type I glass) vial with rubber stopper closed with a cap.
Solvent: 1 ml pre-filled syringe (type I glass) with rubber (type I) tip cap and plunger rubber stopper.
Each pack contains 1 vial of powder, 2 pre-filled syringes with solvent for reconstitution, 1 needle for reconstitution, 18 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles.

6.6 Special precautions for disposal

The powder should only be reconstituted with the solvent provided in the package.
Attach the reconstitution needle to the prefilled syringe. Inject the total contents of solvent into the vial containing the powder.
MENOPUR 600 IU must be reconstituted with one pre-filled syringe with solvent before use.
MENOPUR 1200 IU must be reconstituted with two pre-filled syringes with solvent before use. 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.
The reconstituted solution should not be administered if it contains particles or is not clear.
The single use administration syringes are graduated in FSH/LH units from 37.5 – 600 IU.
Draw up the exact prescribed dose of reconstituted solution from the vial using one of the disposable syringes provided for injection and administer the dose immediately.. Each ml of reconstituted solution contains 600 IU FSH and LH.
Discard the syringe after use.
Each reconstituted MENOPUR 600 IU or 1200 IU vial should be for individual patient use only.
Any unused product or waste material should be disposed in accordance with local requirements.

7. MANUFACTURER

Ferring GmbH Germany

8. LICENSE HOLDER

Ferring Pharmaceuticals Ltd.
8 Hashita St., Industrial Park Caesarea 3088900

9. MARKETING AUTHORISATION NUMBER(S)

Menopur Multidose 600 IU: 147 66 33326
Menopur Multidose 1200 IU: 147 67 33343

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