Version 4.0, 02/2016

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

1. NAME OF THE MEDICINAL PRODUCT

MENOPUR 1200 IU Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MENOPUR 1200 IU: Each vial with powder contains highly purified menotrophin (human menopausal gonadotrophin, HMG) corresponding to follicle stimulating hormone activity FSH 1200 IU and luteinizing hormone activity LH 1200 IU. After reconstitution, 1 ml of the reconstituted solution contains 600 IU of highly purified menotrophin.

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

The active ingredient in MENOPUR is obtained from the urine of postmenopausal women.

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

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 hyperstimulation 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 intracytoplasmic sperm injection (ICSI)).

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.

Posology
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 a protocol using down-regulation with a GnRH agonist, MENOPUR therapy should start approximately 2 weeks after the start of the agonist treatment. In a protocol using down-regulation with a GnRH antagonist, MENOPUR therapy should start on day 2 or 3 of the menstrual cycle. 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.

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).

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

Method of administration
MENOPUR is intended for subcutaneous (S.C.) 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.

General
Shaking should be avoided. The solution should not be used if it contains particles or if it is not clear.

4.3 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 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 MENOPUR 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

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.

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). 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 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 desensitisation, a higher dose of MENOPUR may be necessary to achieve adequate follicular response.

4.6 Fertility, pregnancy and lactation

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 lactating (see section 4.3).

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

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 serious and frequently reported adverse drug reactions reported during treatment with MENOPUR in clinical trials are OHSS, abdominal pain, headache, abdominal distension and injection site pain, with an incidence rate up to 5%. The table below displays the main adverse drug reactions in women treated with MENOPUR in clinical trials distributed by system organ classes (SOCs) 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 (≥ 1/1000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Unknown
Eye disorders				Visual disorders [a]
Gastrointestinal disorders	Abdominal pain, Abdominal distension, nausea, enlarged abdomen	Vomiting, Abdominal discomfort, Diarrhoea		
General disorders and administration site condition	Injection site reactions [b]	Fatigue		Pyrexia, Malaise
Immune system disorders				Hypersensitivity reactions [c]
Investigations				Weight increased
Musculoskeletal & connective tissue disorders				Musculoskeletal pain [d]
Nervous system disorders	Headache	Dizziness		

Reproductive system 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 flush		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 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.

[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.

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 via <the national reporting system> <[to be completed nationally]>

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

MENOPUR is produced from the urine of post menopausal women. 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, 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 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. 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 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 ± 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 ± 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, disodium phosphate heptahydrate (for pH adjustment), phosphoric acid (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

Powder: 3 years
Solvent: 3 years
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. For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

MENOPUR 1200 IU:
Powder: 2 ml colourless glass (type I glass) vial with rubber stopper (halobutyl) closed with a cap.
Solvent: 1 ml pre-filled syringe (type I glass) with rubber tip cap (elastomer) and plunger rubber stopper (halobutyl).

The product is supplied as a pack of 1 vial of powder, 2 pre-filled syringes with solvent for reconstitution, 1 needle for reconstitution and 18 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles.

6.6 Special precautions for disposal and other handling

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 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. Shaking should be avoided.

The single use administration syringes with pre-fixed needle are graduated in FSH/LH units from 37.5 – 600 IU.
Draw up the reconstituted solution from the vial into the administration syringe for injection according to the prescribed dose and administer the dose immediately. Each ml of reconstituted solution contains 600 IU FSH and LH.

Each reconstituted MENOPUR 600 IU or 1200 IU vial should be for individual patient use only.

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

Local Ferring Company
<[To be completed nationally]>

{Name and address}
<{tel}>

<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

Local MA number
<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

<[To be completed nationally]>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING (CARTON)
POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT

MENOPUR 1200 IU, powder and solvent for solution for injection

Menotrophin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One multidose vial of powder contains: Menotrophin (HMG) corresponding to FSH 1200 IU and LH 1200 IU

3. LIST OF EXCIPIENTS

Powder: Lactose monohydrate, polysorbate 20, disodium phosphate heptahydrate (as buffer agents and for pH adjustment), phosphoric acid (for pH adjustment)

Solvent: Metacresol, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
1 vial of powder
2 pre-filled syringes with solvent
1 needle for reconstitution
18 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles.

After reconstitution, 1 ml of the reconstituted solution contains 600 IU highly purified menotrophin.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneaous use.
For multiple injections only
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

MENOPUR 1200 IU must be reconstituted with two pre-filled syringes with solvent before use.

8. EXPIRY DATE

EXP:
After reconstitution, the solution may be stored for a maximum of 28 days.

9. SPECIAL STORAGE CONDITIONS

Prior to reconstitution, store in a refrigerator. Do not freeze..
After reconstitution, do not store above 25°C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution after 28 days.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MENOPUR 1200 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL OF POWDER
POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

MENOPUR 1200 IU, powder for solution for injection

Menotrophin
s.c.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:
After opening: max 28 days.

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1200 IU/vial or 600 IU/ml

6. OTHER

Marketing authorisation holder (to be completed nationally)

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE OF SOLVENT
SOLVENT FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for MENOPUR 600 IU/1200 IU

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.1 mL/pre-filled syringe

6. OTHER

Marketing authorisation holder (to be completed nationally)

PACKAGE LEAFLET

Package leaflet: Information for the user

MENOPUR 1200 IU powder and solvent for solution for injection

Menotrophin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What MENOPUR is and what it is used for

MENOPUR is provided as a powder which must be mixed with liquid (solvent) before it is used. It is given as an injection under the skin.

MENOPUR contains two hormones called follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH are natural hormones produced in both males and females. They help the reproductive organs to work normally. The FSH and LH in MENOPUR are obtained from the urine of postmenopausal women. The active ingredient is highly purified, and is known as menotrophin.

MENOPUR is used to treat female infertility in the following two situations:

i. Women who cannot become pregnant because their ovaries do not produce eggs (including polycystic ovarian disease). MENOPUR is used in women who have already been given a medicine called clomiphene citrate to treat their infertility, but this medicine has not helped.

ii. Women in assisted reproductive technology programmes (ART) (including *in vitro* fertilisation/embryo transfer [IVF/ET], gamete intra-fallopian transfer [GIFT] and intracytoplasmic sperm injection [ICSI]). MENOPUR helps the ovaries to develop many egg sacs (follicles) where an egg might develop (multiple follicular development).

2. What you need to know before you use MENOPUR

Before starting treatment with MENOPUR, you and your partner should be evaluated by a doctor for the causes of your fertility problems. In particular you should be checked for the following conditions so that appropriate treatment can be given:
- Underactive thyroid or adrenal glands
- High levels of a hormone called prolactin (hyperprolactinemia)
- Tumours of the pituitary gland (a gland located on the base of the brain)
- Tumours of the hypothalamus (an area located under the part of the brain called the thalamus)

If you know you have any of the conditions listed above**, please tell your doctor before starting treatment with MENOPUR.**

Do not use MENOPUR
- If you are allergic (hypersensitive) to menotrophin or any of the other ingredients of MENOPUR (listed in section 6)
- If you have tumours of the womb (uterus), ovaries, breasts, or parts of the brain like pituitary gland or hypothalamus
- If you have sacs of fluid known as cysts on your ovaries (ovarian cysts) or enlarged ovaries (unless caused by polycystic ovarian disease)
- If you have any physical defects of the womb (uterus) or other sexual organs
- If you suffer from bleeding from the vagina where the cause is not known
- If you have fibroids (benign tumors) of the womb (uterus)
- If you are pregnant or breastfeeding
- If you have experienced an early menopause

Warnings and precuations
Talk to your doctor
- If you get pain in the abdomen
- If you get swelling in the abdomen
- If you get nausea
- If you get vomiting
- If you get diarrhoea
- If you gain weight
- If you get difficulty breathing
- If you get decreased urination.

Tell your doctor straight away, even if the symptoms develop some days after the last injection has been given. These can be signs of high levels of activity in the ovaries which might become severe.

If these symptoms become severe, the infertility treatment should be stopped and you should receive treatment in hospital.

Keeping to your recommended dose and careful monitoring of your treatment will reduce your chances of getting these symptoms.

If you stop using MENOPUR you might still experience these symptoms. Please contact your doctor immediately if any of these symptoms occur.

While you are being treated with this medicine, your doctor will normally arrange for you to have **ultrasound scans** and sometimes **blood tests** to monitor your response to treatment.

Being treated with hormones like MENOPUR can increase the risk of:
- Ectopic pregnancy (pregnancy outside of the womb) if you have a history of fallopian tube disease
- Miscarriage
- Multiple pregnancy (twins, triplets, etc)
- Congenital malformations (physical defects present in baby at birth).

Some women who have been given infertility treatment with multiple medicine have developed tumours in the ovaries and other reproductive organs. It is not yet known if treatment with hormones like MENOPUR causes these problems.

Blood clot formation inside the blood vessels (veins or arteries) are more likely to occur in women who are pregnant. Infertility treatment can increase the chances of this happening, especially if you are overweight or known with blood clotting disease (thrombophilia) or if you or someone in your family (blood relative) has had blood clots. Tell your doctor if you think this applies to you.

Children
There is no relevent use of MENOPUR in children.

Other medicines and MENOPUR
Please tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Clomiphene citrate is another medicine used in the treatment of infertility. If MENOPUR is used at the same time as clomiphene citrate the effect on the ovaries may be increased.

Pregnancy and breast-feeding
MENOPUR should not be used during pregnancy or breastfeeding.

Driving and using machines
MENOPUR is unlikely to affect your ability to drive and use machines.

Important information about some of the ingredients of MENOPUR
MENOPUR contains less than 1 mmol sodium (23 mg) per dose, so it is essentially 'sodium-free'.

3. How to use MENOPUR

Always take MENOPUR exactly as your doctor has told you. You should check with your doctor if you are not sure.

i. Women who are not ovulating (not producing eggs):
Treatment should start within the first 7 days of the menstrual cycle (day 1 is the first day of your period). Treatment should be given every day for at least 7 days.

The starting dose is normally 75-150 IU daily. This dose may be increased according to your response to the treatment up to a maximum of 225 IU per day. A particular dose should be given for at least 7 days before the dose is changed by your doctor. It is recommended that the dose should be increased by 37.5 IU per adjustment (and not more than 75 IU). The cycle of treatment should be abandoned if there is no response after 4 weeks.

When a good response is obtained a single injection of another hormone called human chorionic gonadotrophin (hCG), at a dose of 5,000 to 10,000 IU, should be given 1 day following the last MENOPUR injection. It is recommended to have sexual intercourse on the day of the hCG injection and the day after. Alternatively, artificial insemination (injection of sperm directly into the womb) may be performed. Your doctor will closely monitor your progress for at least 2 weeks after you have received the hCG injection.

Your doctor will monitor the effect of MENOPUR treatment. Depending on your progress, your doctor may decide to stop treatment with MENOPUR and not give you the hCG injection. In this case, you will be instructed to use a barrier method of contraception (e.g. condom) or not have sexual intercourse until your next period has started.

ii. Women in assisted reproductive technology programs:
If you are also receiving treatment with a GnRH agonist (a medicine which helps a hormone called Gonadotropin Releasing Hormone (GnRH) to work), MENOPUR should be started approximately 2 weeks after the start of the GnRH agonist therapy.
If you are also receiving treatment with a GnRH antagonist, MENOPUR treatment should be started on day 2 or 3 of the menstrual cycle (day 1 is the first day of your period).

MENOPUR should be given every day for at least 5 days. The initial dose of MENOPUR is normally 150 - 225 IU. This dose may be increased according to your response to the treatment up to a maximum of 450 IU

per day. The dose should not be increased by more than 150 IU per adjustment. Normally treatment should not continue for more than 20 days.

If enough egg sacs are present, you will be given a single injection of a medicine called human chorionic gonadotrophin (hCG) at a dose of up to 10,000 IU to induce ovulation (release of an egg).

Your doctor will closely monitor your progress for at least 2 weeks after you have received the hCG injection.

Your doctor will monitor the effect of MENOPUR treatment. Depending on your progress, your doctor may decide to stop treatment with MENOPUR and not give you the hCG injection. In this case, you will be instructed to use a barrier method of contraception (e.g. condom) or not have sexual intercourse until your next period has started.

Instructions for use

If your clinic has asked you to inject MENOPUR yourself, you should follow any instructions they provide.

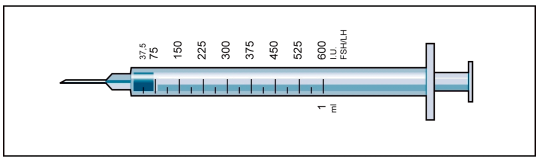
The first injection of MENOPUR should be given under the supervision of a doctor or a nurse.

MENOPUR is provided as a powder in a vial, and must be dissolved with two syringes with solvent before it is injected. The solvents which you should use to dissolve MENOPUR are provided in pre-filled syringes in the package.

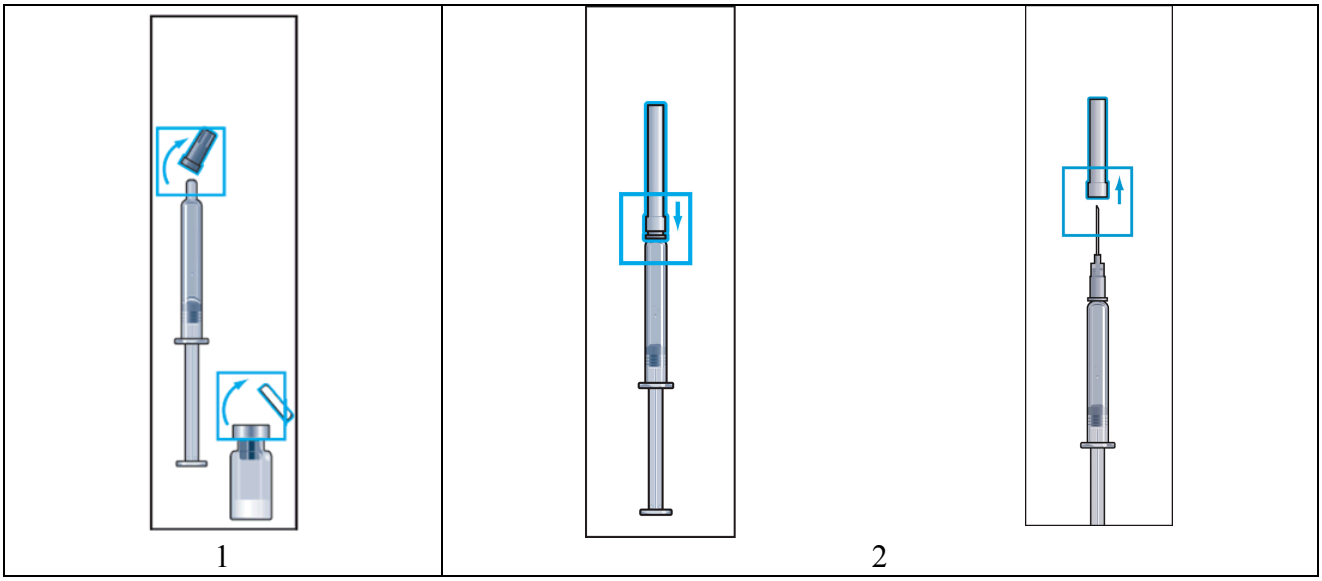
MENOPUR 1200 IU must be dissolved with two pre-filled syringes with solvent before use.

After dissolving the powder with the solvents this vial contains **medication for several days of treatment,** therefore, you need to make sure you only draw up the amount of medication that was prescribed by your doctor.

Your doctor has prescribed you a dose of MENOPUR in IU (units). To obtain the correct dose you should use one of the 18 administration syringes graduated in FSH/LH IU (units) provided.

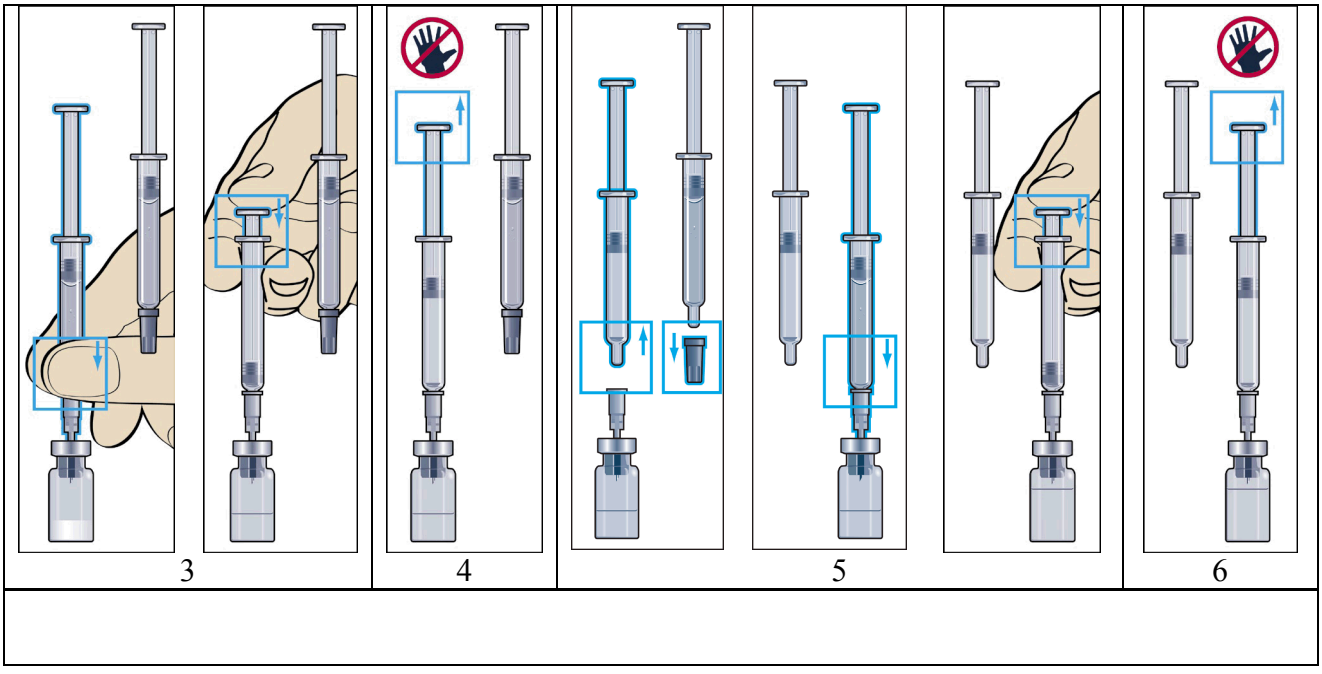


To do this:



1. Remove the protective cap from the vial of powder and the rubber cap from one of the pre-filled syringes with solvent (picture 1).

2. Firmly attach the thick needle (reconstitution needle) to the pre-filled syringe with solvent and remove the protective cap from the needle (picture 2).



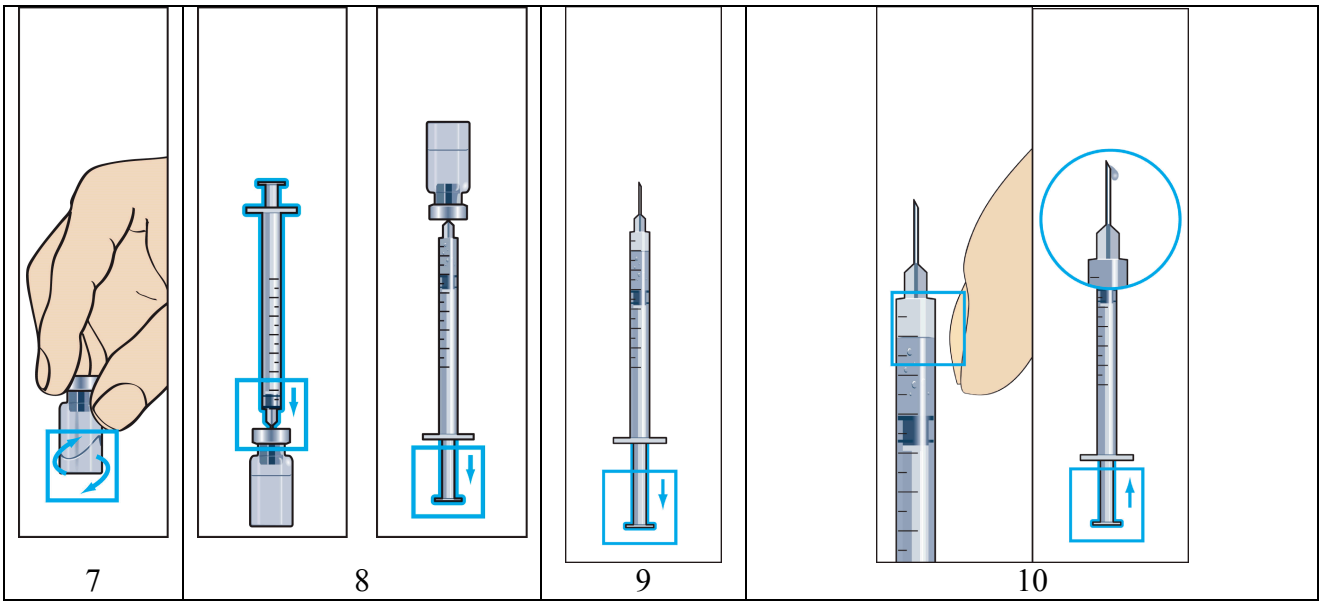
3. Insert the needle vertically through the centre of the rubber stopper of the powder vial and **slowly inject all** of the solvent to avoid creating bubbles (picture 3).

4. When adding the solvent a slight over-pressure is created in the vial. Therefore, let go of the syringe plunger to let it rise up by itself for about 10 seconds. This will remove the over-pressure in the vial (picture 4).

5. Gently remove the syringe from the needle with a twist, leaving the needle in the vial.
Remove the rubber cap from the second pre-filled syringe with solvent and firmly attach the syringe to the needle fixed in the vial. **Slowly inject all** of the solvent to avoid creating bubbles (picture 5).

6. When adding the solvent a slight over-pressure is created in the vial. Therefore, let go of the syringe plunger to let it rise up by itself for about 10 seconds. This will remove the over-pressure in the vial (picture 6).

Remove the syringe and the needle for reconstitution.



7. The powder should quickly dissolve (within 2 minutes) to form a clear solution. Although this normally happens when only few drops of solvent have been added, the entire amount of the solvent should be added. To help the powder dissolve, swirl the solution (picture 7). **Do not shake** as this will cause air bubbles to form.

*If the solution is not clear or if it contains particles it **should not** be used.*

The vial with powder is now dissolved with two syringes with solvent and ready to use.

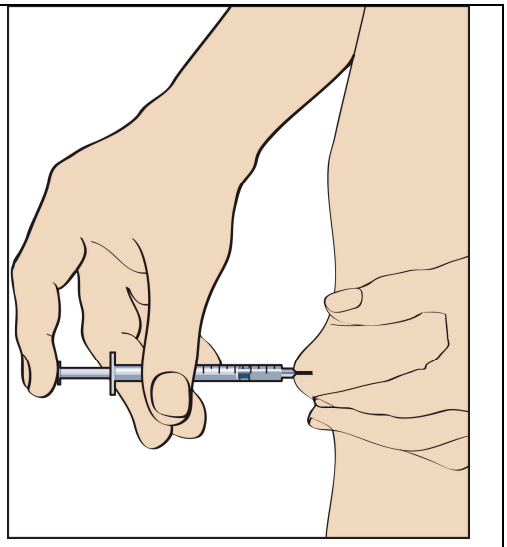
8. Take the administration syringe with pre-fixed needle and insert the needle vertically in the centre of the vial. The administration syringe already contains a small amount of air, which should be injected in the vial above the liquid. Turn the vial upside down and draw the prescribed dose of MENOPUR into the administration syringe for injection (picture 8).

REMEMBER: as this vial contains medication for several days of treatment, you need to make sure you only draw up the amount of medication that was prescribed by your doctor.

9. Remove the syringe from the vial and draw a small amount of air into the syringe (picture 9).

10. Gently flick the administration syringe so that all air bubbles will be collected in the tip (picture 10). Carefully, push out all air and push until the first drop of fluid comes out from the needle.

Your doctor or nurse will tell you where to inject (e.g. front of the thigh, abdomen etc.).
Before injection, disinfect the injection site.



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11. To inject, pinch the skin to produce a fold, and insert the needle in one swift motion at 90 degrees to the body. Press down on the plunger gently to inject the solution (picture 11) and then remove the administration syringe.

After removing the administration syringe, apply pressure to the injection site to stop any bleeding. Gently massaging the injection site will help to disperse the solution under the skin.

Do no put used items into normal domesctic waster; these should be disposed of appropriately.

8. For next injection from the already dissolved MENOPUR solution repeate steps 8 to 11.

If you take more MENOPUR than you should
Please tell a nurse or a doctor

If you forget to take MENOPUR
Do not take a double dose to make up for a forgotten dose. Please tell a nurse or doctor.

4. Possible side effects

Like all medicines, MENOPUR can cause side effects, although not everybody gets them.

Hormone used in treatment of infertility such as MENOPUR may cause **high levels of activity in the ovaries leading to a disease called Ovarian Hyperstimulation Syndrome (OHSS),** especially in women with polycystic ovaries. Symptoms include: **pain in the abdomen, swelling in the abdomen, nausea, vomiting, diarrhoea and weight gain.** In cases of severe OHSS **accumulation of fluid in abdomen, pelvis and/or chest cavity, difficulty in breathing, decreased urination, formation of blood clots in blood vessels (thromboembolism) and twisting of ovaries (ovarian torsion)** have been reported as rare complications. If you experience any of these symptoms contact your doctor immediately, even if they develop some days after the last injection has been given.

Allergic (hypersensitivity) reactions may occur when using this medicine. Symptoms of these reactions might include**: rash, itching, swelling of the throat and difficulty breathing.** If you experience any of these symptoms, contact your doctor immediately.

The following common side effects affect between 1 to 10 of every 100 patients treated:
- Pain in the abdomen
- Headache

- Nausea
- Swelling in the abdomen
- Pelvic pain
- Overstimulation of the ovaries resulting into high levels of activity (ovarian hyperstimulation syndrome)
- Local reactions at the injection site (such as pain, redness, bruising, swelling and/or itching)

The following uncommon side effects affect between 1 to 10 of every 1,000 patients treated:
- Vomiting
- Discomfort in abdomen
- Diarrhoea
- Fatigue
- Dizziness
- Sacs of fluid within ovaries (ovarian cysts)
- Breast complaints (include breast pain, breast tenderness, breast discomfort, nipple pain and breast swelling)
- Hot flush

The following rare side effects affect between 1 to 10 of every 10,000 patients treated:
- Acne
- Rash

In addition to above the following side effects were seen after MENOPUR was marketed and frequency of these side effects is unknown:
- Eyesight disturbances
- Fever
- Feeling sick
- Allergic reactions
- Increase in weight
- Pains in muscle and joint (e.g. back pain, neck pain and pain in arms and legs)
- Twisting of ovary (ovarian torsion) as a complication of increased activity of ovaries due to overstimulation
- Itching
- Hives
- Blood clots as a complication of increased activity of ovaries due to overstimulation

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via <the national reporting system> <[to be completed nationally]> . By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store MENOPUR

Keep this medicine out of sight and reach of children.

Prior to reconstitution store in a refrigerator (2°C – 8°C)**.** Do not freeze.

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

The reconstituted solution should not be administered if it contains particles or is not clear.
Do not use MENOPUR after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not throw away medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What MENOPUR contains

The active substance is highly purified menotrophin (human menopausal gonadotrophin, HMG) corresponding to follicle stimulating hormone activity FSH 1200 IU and luteinizing hormone activity LH 1200 IU.
After reconstitution, 1 ml of the reconstituted solution contains 600 IU highly purified menotrophin.

The other ingredients in the powder are:
Lactose monohydrate
Polysorbate 20
Disodium phosphate heptahydrate (as buffer agents and for pH adjustment)
Phosphoric acid (for pH adjustment)

The ingredients in the solvent are:
Water for injection
Metacresol

What MENOPUR looks like and contents of the pack

MENOPUR is a powder and solvent for solution for injection.

The product is supplied as a pack of 1 vial of powder, 2 pre-filled syringes with solvent for reconstitution, 1 needle for reconstitution and 18 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder is Ferring {local company}
{To be completed nationally}

Manufacturer
Ferring GmbH
Wittland 11, D-24109 Kiel, Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Denmark, Finland, Greece, Norway, Portugal, Sweden: MENOPUR
Italy: MEROPUR

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}.>
<[To be completed nationally]>

<Detailed information on this medicine is available on the web site of {MA/Agency}>

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