

**SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MENOPUR 75 IU powder and solvent for solution for injection.

2. 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 luteinizing hormone activity LH 75 IU.

Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in postmenopausal urine, is present in MENOPUR and contributes to the overall luteinizing hormone 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

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 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.) or intramuscular (I.M.) injection after reconstitution with the solvent provided. 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.

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/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.

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

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).

Lactation

MENOPUR is contraindicated in women who are lactating (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 serious and frequently reported adverse drug reactions reported during treatment with MENOPUR in clinical trials are OHSS, abdominal pain, abdominal distension, headache, 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, mydriasis, 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 contributes to the overall luteinizing hormone (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 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. 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 \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.

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 hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)

Solvent:

Sodium chloride
Hydrochloric acid (for pH-adjustment)
Water for injections.

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: 2 years
Solvent: 3 years

For immediate and single use following reconstitution.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

MENOPUR is available in the following containers and pack sizes:
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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Attach a 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. 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 a 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

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

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 75 IU powder and solvent for solution for injection
Menotrophin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Menotrophin (HMG) corresponding to FSH 75 IU and LH 75 IU.

3. LIST OF EXCIPIENTS

Powder:

Lactose monohydrate
Polysorbate 20
Sodium hydroxide.
Hydrochloric acid to adjust pH

Solvent:

Sodium chloride
Water for Injections
Hydrochloric acid to adjust pH

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
5 vials of powder (75 IU)
5 ampoules of solvent (1 ml)

10 vials of powder (75 IU)
10 ampoules of solvent (1 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous and Intramuscular use.
Must be reconstituted.
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

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze. Store in the original container in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**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 75 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

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

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

MENOPUR 75 IU powder for solution for injection

Menotrophin (75 IU FSH + 75 IU LH)
s.c and i.m.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Marketing authorisation holder (to be completed nationally)

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
SOLVENT AMPOULE
SOLVENT FOR SOLUTION FOR INJECTION

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

Solvent for MENOPUR 75 IU
s.c. and i.m.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

Marketing Authorisation holder (to be completed nationally)

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

MENOPUR 75 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
2. What you need to know before you use MENOPUR
3. How to use MENOPUR
4. Possible side effects
5. How to store MENOPUR
6. Content of the pack and other information

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 or in the muscle.

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 any other 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 cysts (ovarian cysts) on your ovaries 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 tumours) of the womb (uterus)
- If you are pregnant or breastfeeding
- If you have experienced an early menopause

Warnings and precautions

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 diarrhea
- 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 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 relevant use of MENOPUR in children.

Other medicines and MENOPUR

Tell your doctor if you are taking or 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 use 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 (1 to 2 vial of powder) but this may be adjusted depending on your response (up to a maximum of 225 IU – 3 vials of powders 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 (half a vial of powder) 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 reproduction 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 (2 or 3 vials of powder). This dose may be increased according to your response to the treatment up to a maximum of 450 IU (6 vials of powder) 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.

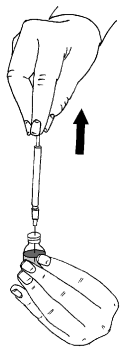
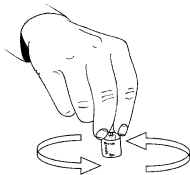
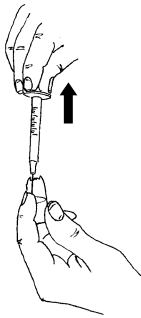
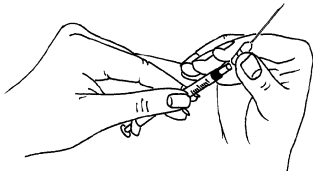
INSTRUCTIONS FOR USE

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.

DISSOLVING MENOPUR:

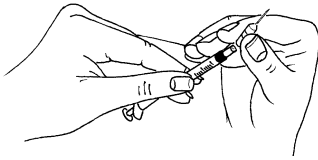
MENOPUR is provided as a powder, and should be dissolved before use. The solvent (liquid) that you should use for dissolving is provided together with the powder. Dissolve MENOPUR right before use. Do as follows:



- Firmly attach a long, thick needle (drawing up/reconstitution needle) to the syringe.
- Break the liquid (solvent) ampoule with the dot pointing towards yourself
- Insert the needle in the liquid ampoule.
- Draw up all of the liquid from the ampoule into the syringe.
- Insert the needle through the rubber stopper of the powder vial and slowly inject all of the liquid. Aim at the side of the vial, to avoid creating bubbles.
- The powder should quickly dissolve (within 2 minutes) to form a clear solution. This normally happens when only few drops of solvent have been added.
- To help the powder dissolve, swirl the solution. **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.*
- Draw up the solution back into the syringe.

If you have been prescribed more than one vial of MENOPUR powder per injection, you can draw up the solution (the first MENOPUR dilution) back into the syringe and inject it into a second vial of powder. You can do this with up to three vials of powder in total – but only do as your doctor has told you.

INJECTING MENOPUR:



- Once you have your prescribed dose drawn up into the syringe, change the needle to a short, thin needle (the injection needle).
- Turn the syringe with the needle upwards and flick it gently so that any air bubbles collect in the tip. Depress the plunger carefully until the first drop of fluid comes out.

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



- 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 to inject the solution, and then remove the needle.

● After removing the 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 not put used items into normal domestic waste; these should be disposed of appropriately.

If you take more MENOPUR than you should

Please tell a nurse or 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.

Treatment with 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

If you get any side effects, talk to your doctor or nurse. This includes any side effects not listed in this leaflet.

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

Do not store above 25°C. Do not freeze.
Store in the original package in order to protect from light.

For immediate and single use following reconstitution.

Keep this medicine out of sight and reach of children.

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 any medicines 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 75 IU and luteinizing hormone activity LH 75 IU.

The other ingredients in the powder are:

- Lactose monohydrate
- Polysorbate 20
- Sodium hydroxide
- Hydrochloride acid

The ingredients in the solvent are:

- Water
- Hydrochloric acid
- Sodium chloride

What MENOPUR looks like and contents of the pack

MENOPUR is a powder and solvent for solution for injection.

The carton contains five or ten clear glass vials which contain a white to off-white powder. The carton also contains an equal number of clear glass ampoules containing a colourless solvent.

Not all pack sizes may be marketed.

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