## 1. NAME OF THE MEDICINAL PRODUCT
**MENOPUR®, Powder and solvent for solution for injection, 75 IU**

## 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. After reconstitution of one vial, 1 mL of the reconstituted solution contains 75 IU of highly purified menotrophin.

Reconstituted solution: The mixed powder and solvent has a pH value of 5.0-7.0 (release limit) and pH value of 5.0-8.0 (shelf-life limit).

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

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 and 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)).

Sterility in females with hypo- or normogonadotropic ovarian insufficiency: Stimulation of follicular growth.

### 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.

The inter-individual variations in the response of the ovaries to exogenous gonadotrophins is high. 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 objective 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) (e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)):**
In a protocol using down-regulation with a GnRH agonists, MENOPUR® therapy should start approximately 2 weeks after the start of 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.

**Women with hypo- or normogonadotropic ovarian insufficiency:**
The dose of MENOPUR® required to induce follicular growth in normo- or hypogonadotrophic women must be adjusted individually for each patient. The amount depends on ovarian reaction and should be checked by ultra-sound examinations of the ovaries and measuring estradiol levels. If the MENOPUR® dosage is too high for the treated individual, multiple uni and bilateral follicle growth can occur.

MENOPUR® is administered intramuscularly or subcutaneously and in general, the therapy is begun with a daily dosage of corresponding to 75-150 IU FSH (1-2 vials MENOPUR® per day). If there is no ovarian reaction, the dose can be gradually increased until there is evidence of estradiol secretion or follicular growth. The dose of HMG should be maintained until the pre-ovulation estradiol serum level is achieved. The dose should be reduced if the level increases too rapidly.

As a measure of follicle maturity the following values can be taken:
- total urinary oestrogen: 75-150 micrograms (270-540 nmol)/24 hours
- plasma 17 beta-oestradiol: 400-800 picograms/ml (1500-3000 pmol/L).

To induce ovulation, 5,000-10,000 IU hCG should be administered by intramuscular injection 1-2 days after the last dose of HMG.

*Note:*
Unintentional hyperstimulation of the ovaries can be induced by the administration of hCG after an excessive dose of MENOPUR®. Duration of treatment depends on the individual situation of the patient (estradiol level, ultra-sound). For intramuscular or subcutaneous injection after dissolving the dry substance in the solvent included.

*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.

*Elderly population (more than 65 years of age)*
There is no relevant use of MENOPUR® in the elderly population.

Method of administration
MENOPUR® 75 IU 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.

The reconstituted solution should be clear and colourless by visual inspection.

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

**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**
The luteinising hormone activity of MENOPUR® is almost totally contributed by Human Chorionic Gonadotrophin (hCG), which has a longer plasma half-life than Luteinising Hormone. As a consequence, the duration of luteinizing hormone activity of MENOPUR® may differ from that of recombinant products. MENOPUR® is a potent gonadotropic substance capable of causing mild to severe adverse reactions, and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonadotrophin therapy requires a certain time commitment by physicians and supportive health professionals, and calls for monitoring of ovarian response with ultrasound, alone or in combination with measurement of serum oestradiol levels, on a regular basis. There is considerable inter-patient variability in response to menotrophin administration, with a poor response to menotrophin in some patients. The lowest effective dose in relation to the treatment objective should be used. The first injection of MENOPUR® should be performed under direct medical supervision.

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.

Patients undergoing stimulation of follicular growth, whether in the frame of a treatment for anovulatory infertility or ART procedures may experience ovarian enlargement or develop hyperstimulation. Adherence to recommended MENOPUR® dosage and regimen of administration, and careful monitoring of therapy will minimise the incidence of such events. Acute interpretation of the indices of follicle development and maturation requires a physician who is experienced in the interpretation of the relevant tests.

Ovarian Hyperstimulation Syndrome (OHSS)
OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS is a syndrome that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and rarely, in the pericardial cavities.

The following symptoms may be observed in 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. Other reported risk factors that increase the risk of developing OHSS include previous episodes of OHSS, many follicles and high level of oestradiol.

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 loss
The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ART procedures than in the normal population.

Ectopic pregnancy
Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatment. The prevalence of ectopic pregnancy after IVF has been reported to be 2 to 5%, as compared to 1 to 1.5% in the general population.

Reproductive system neoplasms

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established if treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.

Congenital malformation
The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and multiple pregnancies.

Thromboembolic events
Women with generally recognised risk factors for thromboembolic events, such as personal or family history, severe obesity (Body Mass Index > 30 kg/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 desensitization, a higher dose of MENOPUR® may be necessary to achieve adequate follicular response.

**4.6 Fertility, pregnancy and lactation**
Fertility
MENOPUR® is indicated for use in infertility (see section 4.1).

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

There are no or limited amount of data from the use of menotrophins in pregnant women. Although no adequate animal studies have been conducted with MENOPUR®, based on its pharmacology and reproductive studies conducted with similar products, an increase in embryonic resorptions and post-implantation loss may be expected at clinically relevant doses.

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 frequently reported adverse drug reactions (ADR) during treatment with MENOPUR® in clinical trials are Ovarian Hyperstimulation Syndrome(OHSS), headache, pelvic pain, pelvic discomfort, abdominal pain, abdominal distension, nausea and injection site reactions. 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. Further, the ADRs seen during post-marketing experience are mentioned with unknown frequency.

| **System Organ Class** | **Common (> 1/100 to < 1/10)** | **Uncommon (> 1/1,000 to < 1/100)** | **Rare (> 1/10,000 to < 1/1,000)** | **Unknown** |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Eye disorders | | | | Visual impairment |
| Gastrointestinal disorders | Abdominal pain, Abdominal distension, Nausea | Vomiting, Abdominal discomfort, Diarrhoea | | |
| General disorders and administration site condition | Injection site reactions[a] | Fatigue | | Pyrexia, Malaise |
| Immune system disorders | | | | Hypersensitivity reactions[b] |
| Investigations | | | | Weight increased |
| 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 subcutaneous tissue disorders | | | Acne, Rash | Pruritus, Urticaria |
| Vascular Disorders | | Hot flush | | Thromboembolism[d] |

[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. Refer to section 4.5.
[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.

**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

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.

MENOPUR®, administered for 7 to 20 days, produces ovarian follicular growth and maturation in women who do not have primary ovarian failure. Treatment with MENOPUR® in most instances results only in follicular growth and maturation. When sufficient follicular maturation has occurred, hCG must be given to induce ovulation.

Mechanism of action

MENOPUR® is produced from the urine of postmenopausal 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.

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 patients´ 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 $C_{max}$ (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 ($T_{max}$) within 7 hours for both routes of administration. After repeated administration, FSH was eliminated with a half-life ($T_{1/2}$) (mean ± SD) of 30 ± 11 hours and 27 ± 9 hours for the SC and IM administration, respectively. Although the individual LH concentration versus time curves show an increase in the LH concentration after dosing with MENOPUR®, the data available were too sparse to be subjected to a pharmacokinetic analysis.

Menotrophin is mainly excreted through the kidneys with a contribution through the liver.

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

**5.3 Preclinical safety data**
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. PHARACEUTICAL PARTICULARS

**6.1 List of excipients**
Powder:
Lactose monohydrate, polysorbate 20, sodium hydroxide, hydrochloric acid

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

**6.2 Incompatibilities**
MENOPUR® should not be administered in the same injection with other 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 30˚C. Do not freeze. Store in the original container 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) vials with rubber stopper closed with a cap.
Solvent: 1 mL colourless glass (Type I) ampoule.

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

**6.6 Precautions for disposal**
The powder should only be reconstituted with the solvent provided in the package. 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.

**6.7 Other handling information**
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. When the solvent needle pierces the vial there is a slight vacuum inside the vial which may lead to the powder completely dissolving with only a few drops of solvent. This may give the false impression that there was no powder in the vial, please be sure to add the entire solvent and proceed to the next step of administration. 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.

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**DATE OF REVISION**
22 Sep 2023