Menopur 75IU

Summary of Product Characteristics Updated 03-Jun-2016 | Ferring Pharmaceuticals Ltd

1. Name of the medicinal product

MENOPUR®

2. Qualitative and quantitative composition

Active ingredient

Each vial with dry substance contains highly purified menotrophin (human menopausal gonadotrophin, HMG) corresponding to 75 IU human follicle stimulating hormone (FSH) and 75 IU human luteinising hormone (LH).

3. Pharmaceutical form

Powder for injection; and solvent for parenteral use.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of female and male infertility in the following groups of patients:

- Anovulatory women: MENOPUR can be used to stimulate follicle development in amenorrhoeic patients. Clomiphene (or a similar ovulation inducing agent which influences steroid feed-back mechanisms) is the preferred treatment for women with a variety of menstrual cycle disturbances, including luteal phase insufficiency with anovulatory cycles and with normal prolactin, and also amenorrhoeic patients with evidence of endogenous oestrogen production but normal prolactin and normal gonadotrophin levels. Non-responders may then be selected for menotrophin therapy.

- Women undergoing superovulation within a medically assisted fertilisation programme: MENOPUR can be used to induce multiple follicular development in patients undergoing an assisted conception technique such as in-vitro fertilisation (IVF).

- Hypogonadotrophic hypogonadism in men: MENOPUR may be given in combination with human chorionic gonadotrophin (e.g. Choragon) for the stimulation of spermatogenesis. Patients with primary testicular failure are usually unresponsive.

4.2 Posology and method of administration

Anovulatory infertility:

Menotrophin is administered to induce follicular maturation and is followed by treatment with chorionic gonadotrophin to stimulate ovulation and corpus luteum formation.

The dosage and schedule of treatment must be determined according to the needs of each patient. Response is monitored by studying the patient's urinary oestrogen excretion or by ultrasound visualisation of follicles. Menotrophin may be given daily by either intramuscular or subcutaneous injection to provide a dose of 75 to 150 units of FSH and 75 to 150 units of LH, and gradually adjusted if necessary until an adequate response is achieved, followed after 1 or 2 days by chorionic gonadotrophin. In menstruating patients, treatment should be started within the first 7 days of the menstrual cycle. The treatment course should be abandoned if no response is seen in 3 weeks. This treatment cycle may be repeated at least twice more if necessary. Alternatively, three equal doses of menotrophin, each providing 225 to 375 units of FSH with 225 to 375 units of LH, may be given on alternate days followed by chorionic gonadotrophin one week after the first dose.

In the daily therapy schedule, the dose is gradually increased until oestrogen levels start to rise. The effective dose is then maintained until adequate pre-ovulatory oestrogen levels are reached. If oestrogen levels rise too rapidly, the dose should be decreased.

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).

When adequate pre-ovulatory oestrogen levels have been reached, administration of MENOPUR is stopped, and ovulation may then be induced by administering human chorionic gonadotrophin at a dose of 5000 - 10000 IU.

Women undergoing superovulation in IVF or other assisted conception techniques:

In in-vitro fertilisation procedures or other assisted conception techniques menotrophin is used in conjunction with chorionic gonadotrophin and sometimes also clomiphene citrate or a gonadorelin agonist. Stimulation of follicular growth is produced by menotrophin in a dose providing 75 to 300 units of FSH with 75 to 300 units of LH daily. Treatment with menotrophin, either alone or in conjunction with clomiphene or a gonadorelin agonist, is continued until an adequate response is obtained and the final injection of menotrophin is followed 1 or 2 days later with up to 10000 units of chorionic gonadotrophin.

Maturation of follicles is monitored by measurement of oestrogen levels, ultrasound and/or clinical evaluation of oestrogen activity. It is recommended there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500 pmol/L (920 picograms/ml). Egg maturation occurs by administration of human chorionic gonadotrophin in a dose of 5000-10000 IU, 30 - 40 hours after the last MENOPUR injection. Human chorionic gonadotrophin should not be administered if these criteria have not been met. Egg retrieval is carried out 32 - 36 hours after the human chorionic gonadotrophin injection.

Male infertility:

Spermatogenesis is stimulated with chorionic gonadotrophin (1000 – 2000 IU two to three times a week) and then menotrophin is given in a dose of 75 or 150 units of FSH with 75 or 150 units of LH two or three times weekly. Treatment should be continued for at least 3 or 4 months.

Children:

Not recommended for use in children.

Elderly:

Not recommended for use in the elderly.

Method of Administration:

By intramuscular or subcutaneous use.

The dry substance must be reconstituted with the diluent prior to use.

4.3 Contraindications

Men and Women

MENOPUR is contraindicated in men and women with:

- Tumours of the pituitary or hypothalamic glands

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

Men

- Tumours in the testes

- Prostate carcinoma

Women

- Ovarian, uterine or mammary carcinoma

- Pregnancy and lactation

- Gynaecological haemorrhage of unknown aetiology

- Ovarian cysts or enlarged ovaries not due to polycystic ovarian disease.

In the following situations treatment outcome is unlikely to be favourable, and therefore MENOPUR should not be administered:

- Primary ovarian failure

- Malformation of sexual organs incompatible with pregnancy

- Fibroid tumours of the uterus incompatible with pregnancy

- Structural abnormalities in which a satisfactory outcome cannot be expected, for example, tubal occlusion (unless superovulation is to be induced for IVF), ovarian dysgenesis, absent uterus or premature menopause.

4.4 Special warnings and precautions for use

MENOPUR is a potent gonadotropic substance capable of causing mild to severe adverse reactions, and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

In the treatment of female infertility, ovarian activity should be checked (by ultrasound and plasma 17 beta-oestradiol measurement) prior to MENOPUR administration. During treatment, these tests and urinary oestrogen measurement should be carried out at regular intervals, until stimulation occurs. Close supervision is imperative during treatment. See “posology and administration” for optimum response levels of urinary oestrogen and plasma 17 beta-oestradiol. Values below these ranges may indicate inadequate follicular development.

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 severe form OHSS may be life-threatening and is characterised by large ovarian cysts (prone to rupture), acute abdominal pain, ascites, very often hydrothorax and occasionally thromboembolic phenomena. Other symptoms that may be observed include: abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, haemoperitoneum, pleural effusions and acute pulmonary distress.

If urinary oestrogen levels exceed 540 nmol (150 micrograms)/24 hours, or if plasma 17 beta-oestradiol levels exceed 3000 pmol/L (800 picograms/ml), or if there is any steep rise in values, there is an increased risk of hyperstimulation and MENOPUR treatment should be immediately discontinued and human chorionic gonadotrophin withheld. Ultrasound will reveal any excessive follicular development and unintentional hyperstimulation. In the event of hyperstimulation, the patient should refrain from sexual intercourse or to use barrier contraception methods for at least 4 days. OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event, therefore patients should be followed for at least two weeks after the hCG administration.

If during ultrasound, several mature follicles are visualised, human chorionic gonadotrophin should not be given as there is a risk of multiple ovulation and the occurrence of hyperstimulation syndrome.

Adherence to recommended MENOPUR dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy (see sections 4.2 and 4.8). Patients undergoing superovulation may be at an increased risk of developing hyperstimulation in view of the excessive oestrogen response and multiple follicular development. In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation.

OHSS may be more severe and more protracted if pregnancy occurs. Most often, OHSS occurs after hormonal treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses.

If severe OHSS occurs, gonadotrophin treatment should be stopped if still ongoing, the patient hospitalised and specific therapy for OHSS started.

This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

Multiple pregnancy

Multiple pregnancy, especially high order, carries an increased risk of adverse maternal and perinatal outcomes.

In patients undergoing 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 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

In women with generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with gonadotrophins may further increase the risk. 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 Pregnancy and lactation

MENOPUR should not be given during pregnancy or to lactating mothers.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The most frequently reported adverse drug reactions during treatment with MENOPUR in clinical trials are ovarian hyperstimulation, abdominal pain, headache, enlarged abdomen, inflammation at the injection site, pain at the injection site and nausea, with an incidence rate between 2% and 7%. The table below displays the main adverse drug reactions in women treated with MENOPUR in clinical trials according to body system and frequency.

Body System	Frequency	Adverse Drug Reaction
Central/peripheral nervous system disorders	Common (>1/100 <1/10)	Headache
Gastro-intestinal disorders	Common (>1/100 <1/10)	Abdominal pain, enlarged abdomen, nausea and vomiting
Female reproductive disorders	Common (>1/100 <1/10)	Ovarian hyperstimulation

Application site disorders	Common (>1/100 <1/10)	Inflammation at injection site, pain at injection site
Vascular (extracardiac) disorders	Uncommon (>1/1,000 <1/100)	Deep vein thrombosis

In very rare cases, long term use of menotrophin can lead to the formation of antibodies making treatment ineffectual.

Very rare cases of allergic reactions, localised or generalised, and delayed-type hypersensitivity have been reported after treatment with gonadotrophin containing products.

4.9 Overdose

The acute toxicity of menotrophin has been shown to be very low. However, too high a dosage for more than one day may lead to hyperstimulation, which is categorised as mild, moderate or severe. Symptoms of overdosage usually appear 3 - 6 days after treatment with human chorionic gonadotrophin.

Mild hyperstimulation - Symptoms include some abdominal swelling and pain, ovaries enlarged to about 5cm diameter. Therapy - rest; careful observation and symptomatic relief. Ovarian enlargement declines rapidly.

Moderate hyperstimulation - Symptoms include more pronounced abdominal distension and pain, nausea, vomiting, occasional diarrhoea, ovaries enlarged up to 12cm diameter. Therapy - bed rest; close observation especially in the case of conception occurring, to detect any progression to severe hyperstimulation.

Pelvic examination of enlarged ovaries should be gentle in order to avoid rupture of the cysts. Symptoms subside spontaneously over 2 - 3 weeks.

Severe hyperstimulation - This is a rare but serious complication - symptoms include pronounced abdominal distension and pain, ascites, pleural effusion, decreased blood volume, reduced urine output, electrolyte imbalance and sometimes shock, ovaries enlarge to in excess of 12cm diameter. Therapy - hospitalisation; treatment should be conservative and concentrate on restoring blood volume and preventing shock. Acute symptoms subside over several days and ovaries return to normal over 20 - 40 days if conception does not occur - symptoms may be prolonged if conception occurs.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Menotrophin is a gonadotrophin extracted from the urine of postmenopausal women and having both luteinising hormone and follicle stimulating hormone activity. It is given by intramuscular or subcutaneous injection in the treatment of male and female infertility.

Menotrophin (HMG) directly affects the ovaries and the testes. HMG has a gametropic and steroidogenic effect.

In the ovaries, the FSH-component in HMG induces an increase in the number of growing follicles and stimulates their development. FSH increases the production of oestradiol in the granulosa cells by aromatising androgens that originate in the Theca cells under the influence of the LH-component.

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

5.2 Pharmacokinetic properties

HMG is not effective when taken orally and is injected either intramuscularly or subcutaneously. The biological effectiveness of HMG is mainly due to its FSH content. The pharmacokinetics of HMG following intramuscular or subcutaneous administration show great individual variation. The maximum serum level of FSH is reached approximately 18 hours after intramuscular injection and 12 hours after subcutaneous injection. After that, the serum level decreases by a half-life of approximately 55 hours following intramuscular administration and 50 hours following subcutaneous administration.

Excretion of HMG, following administration, is predominantly renal.

5.3 Preclinical safety data

Toxic effects caused by HMG are unknown in humans.

There is no evidence of teratogenic, mutagenic or carcinogenic activity of HMG. Antibodies against HMG can be built up in single cases following repeated cyclical administration of HMG, causing the treatment to be ineffectual.

6. Pharmaceutical particulars

6.1 List of excipients

Dry substance:	lactose, polysorbate 20, sodium hydroxide and hydrochloric acid for pH-adjustment.
Solvent:	isotonic sodium chloride solution, dilute hydrochloric acid for pH adjustment.

6.2 Incompatibilities

None known.

6.3 Shelf life

Two years as packaged for sale.

The reconstituted product should be used immediately and any remaining solution should be discarded.

6.4 Special precautions for storage

Protect from light. Store at a temperature not exceeding 25°C.

6.5 Nature and contents of container

Dry substance: 2ml glass vial

The product is supplied in packs of 1, 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 dry substance must be reconstituted with the diluent prior to use.

Use immediately after reconstitution.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

PL 03194/0074

9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text

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