**Product Monograph**

**Including Patient Medication Information**

# [Pr]MENOPUR®

Menotropins for Injection

Human urine-derived

Powder for solution by subcutaneous injection from vial

75 IU / Vial (75 IU FSH / 75 IU LH)

Gonadotropins for Infertility

Ferring Inc.

200 Yorkland Boulevard, Suite 500

Toronto, Ontario

M2J 5C1

Date of Authorization:
March 23, 2026

Control Number: 299678

## Recent Major Label Changes

| |
|---|
| None at time of the most recent authorization |

## Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

## Part 1: Healthcare Professional Information

### 1. Indications

MENOPUR (menotropins for injection) is indicated for:

- The development of multiple follicles and pregnancy in the ovulatory patient participating in an ART (Assisted Reproductive Technologies) program.

***Selection of Patients***

- A thorough gynecologic and endocrinologic evaluation, including an assessment of pelvic anatomy, must be performed before treatment with MENOPUR. Patients with tubal obstruction should receive MENOPUR only if enrolled in an *in vitro* fertilization (IVF) program.
- Primary ovarian failure should be excluded by the determination of gonadotropin levels.
- Careful examination should be made to rule out the presence of an early pregnancy.
- Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of ovulatory disorders. A thorough diagnostic evaluation should always be performed in patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities before starting MENOPUR therapy.
- Evaluation of the partner's fertility potential should be included in the work-up.

### 1.1. Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### 1.2. Geriatrics

Geriatrics (≥65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

### 2. Contraindications

MENOPUR is contraindicated in women who have:

- A high FSH (follicle stimulating hormone) level indicating primary ovarian failure.
- Uncontrolled thyroid or adrenal dysfunction.
- An organic intracranial lesion such as a pituitary tumour.
- Abnormal vaginal bleeding of undetermined origin.
- Ovarian cysts or enlargement not due to polycystic ovarian syndrome.
- Prior hypersensitivity to menotropins or MENOPUR or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For complete list, see 6 Dosage Forms, Strengths, Composition, and Packaging section of the Product Monograph.
- MENOPUR is not indicated in women who are pregnant or breastfeeding. There are limited human data on the effects of menotropins when administered during pregnancy.

- Sex hormone dependent tumours of reproductive tract and accessory organs.

## 4. Dosage and Administration

### 4.1. Dosing Considerations

There are great inter-individual variations in response of the ovaries to exogenous gonadotropins. 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 gonadotropin-releasing hormone (GnRH) agonist or antagonist. Recommendations about dosage and duration of treatment may change depending on the actual treatment protocols.

To minimize the hazard associated with the occasional abnormal ovarian enlargement which may occur with MENOPUR therapy, the lowest dose consistent with the expectation of good results should be used. MENOPUR should be administered subcutaneously until adequate follicular development is indicated by ultrasound alone or in combination with measurement of serum estradiol levels.

### 4.2. Recommended Dose and Dosage Adjustment

***Assisted Reproductive***

The recommended initial dose of MENOPUR for patients who have received a GnRH antagonist or GnRH agonist for pituitary suppression is 225 IU. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results), subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every two days and should not exceed 150 IU per adjustment. The maximum daily dose of MENOPUR given should not exceed 450 IU and dosing beyond 20 days is not recommended.

Once adequate follicular development is evident, additional Human Chorionic Gonadotropin (hCG) (5000 – 10,000 USP units) should be administered to induce final follicular maturation in preparation for oocyte retrieval. The administration of hCG for triggering of final follicular maturation must be withheld in cases where the ovaries are abnormally enlarged on the last day of therapy. This should reduce the chance of developing ovarian hyperstimulation syndrome (OHSS).

Health Canada has not authorized an indication for pediatric use (<18 years of age) (see 1.1 Pediatrics).

### 4.3. Reconstitution

Dissolve the contents of one to six vials of MENOPUR in 1 mL of sterile saline and ADMINISTER SUBCUTANEOUSLY immediately. Any unused reconstituted material should be discarded.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Table 1 – Reconstitution: daily dosing with 1 to 6 MENOPUR vials using 1 mL of diluent**

| MENOPUR Vial # | Vial Size | Volume of Diluent To Be Added to Vial | Approximate Available Volume | Concentration Per mL |
|---|---|---|---|---|
| 1 | 75 IU | 1 mL diluent | 1 mL | 75 IU |
| 2 | 75 IU | 1 mL solution from MENOPUR vial #1 | 1 mL | 150 IU |
| 3 | 75 IU | 1 mL solution from MENOPUR vial #2 | 1 mL | 225 IU |
| 4 | 75 IU | 1 mL solution from MENOPUR vial #3 | 1 mL | 300 IU |
| 5 | 75 IU | 1 mL solution from MENOPUR vial #4 | 1 mL | 375 IU |
| 6 | 75 IU | 1 mL solution from MENOPUR vial #5 | 1 mL | 450 IU |

***Recommended storage period after reconstitution***

None. The reconstituted product must be used immediately.

For additional storage information, see 11 Storage, Stability, and Disposal.

### 4.4. Administration

The lower abdomen (alternating sides) should be used for subcutaneous administration.

See the Patient Medication Information for detailed information on preparing and administering MENOPUR.

### 4.5. Missed Dose

If the patient misses a dose, the patient should be advised to take the missed dose and not to double dose.

## 5. Overdose

Aside from possible ovarian hyperstimulation (see 7 Warnings and Precautions), little is known concerning the consequences of acute overdosage with MENOPUR.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

## 6. Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

**Table 2 – Dosage Forms, Strengths, and Composition**

| Route of Administration | Dosage Form/ Strength/Composition | Non-Medicinal Ingredients |
|---|---|---|
| Subcutaneous (SC) injection | Lyophilized powder for reconstitution and injection; 75 IU menotropins / vial (75 IU FSH bioactivity and 75 IU LH bioactivity) | Lactose Monohydrate, Polysorbate 20 Sodium Phosphate Buffer (sodium phosphate dibasic heptahydrate, and phosphoric acid) |
| FSH = follicle stimulating hormone<br>LH = luteinizing hormone | | |

**Description**

MENOPUR (menotropins for injection) is a preparation of gonadotropins containing follicle stimulating hormone (FSH), luteinizing hormone (LH) and human chorionic gonadotropin (hCG), which has undergone additional steps of purification.

The reconstituted solution (1 mL) using one vial only contains 75 IU of highly purified menotropins (human menopausal gonadotropin, hMG). Each vial with powder contains hMG corresponding to 75 IU FSH bioactivity and 75 IU LH bioactivity in a 1:1 ratio.

MENOPUR (menotropins for injection) is supplied in sterile vials as a lyophilized, white to off-white powder or pellets.

MENOPUR is available in cartons of 5 vials, or as a kit containing 5 vials of MENOPUR and 5 vials of 0.9% Sodium Chloride Injection, USP per carton.

## 7. Warnings and Precautions

### General

MENOPUR is a drug that should only be used by physicians who are thoroughly familiar with infertility problems. It is a potent gonadotropic substance, capable of causing mild to severe adverse reactions in women. Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and its use requires the availability of appropriate monitoring facilities (see Monitoring and Laboratory Tests).

Careful attention should be given to the diagnosis of infertility in the selection of candidates for MENOPUR therapy (see 1 Indications – *Selection of Patient*).

The drug substance of this drug product is manufactured from human urine. Although the risk is theoretical, and no case of transmission of an infectious agent linked to the use of urine-derived gonadotropins has ever been identified, the risk of transmitting infectious agents cannot be completely excluded.

***Information for Patients***

Prior to therapy with MENOPUR, patients should be informed of the duration of treatment and the monitoring of their condition that will be required. Possible adverse reactions (see 8 Adverse Reactions) and the risk of multiple births should also be discussed.

### Carcinogenesis and Genotoxicity

Long-term toxicity studies in animals have not been performed to evaluate the carcinogenic potential of menotropins.

### Hepatic/Biliary/Pancreatic

The safety and efficacy of MENOPUR in hepatic insufficiency has not been studied.

### Immune

Local and generalized allergic reactions are known adverse reactions that may be associated with administration of gonadotropin preparations. Two events of anaphylaxis and one event of allergic reaction (hypersensitivity) have been reported from post-market experience.

### Monitoring and Laboratory Tests

The combination of both estradiol levels and ultrasonography are useful for monitoring the growth and development of follicles, timing of hCG administration for triggering of final follicular maturation, as well as minimizing the risk of the OHSS and multiple gestations.

The clinical confirmation of ovulation is determined by:

(a) A rise in basal body temperature;

(b) Increase in serum progesterone; and

(c) Menstruation following the shift in basal body temperature.

When used in conjunction with indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation may include the following:

(a) Fluid in the cul-de-sac;

(b) Ovarian stigmata; and

(c) Collapsed follicle.

Because of the subjectivity of the various tests for the determination of follicular maturation and ovulation, it cannot be over-emphasized that the physician should choose tests with which he/she is thoroughly familiar.

### Overstimulation of the Ovary during MENOPUR Therapy

***Ovarian Hyperstimulation Syndrome (OHSS)***: OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly to become a serious medical event. It is characterized by an apparent dramatic increase in vascular permeability, which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see Respiratory and Cardiovascular). Transient liver function test

abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with the OHSS. In the IVF clinical study, 0399E, OHSS occurred in 7.2% of the 373 MENOPUR treated women.

Cases of OHSS are more common, more severe and more protracted if pregnancy occurs. OHSS develops rapidly; therefore, patients should be followed for at least two weeks after hCG administration for triggering of final follicular maturation. Most often, OHSS occurs after 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 there is evidence that OHSS may be developing prior to triggering for final follicular maturation (see Monitoring and Laboratory Tests above), the administration of hCG for triggering of final follicular maturation should be withheld.

If severe OHSS occurs, treatment must be stopped, and the patient should be hospitalized.

A physician experienced in the management of the syndrome, or who is experienced in the management of fluid and electrolyte imbalances, should be consulted.

***Ovarian Enlargement***: Mild to moderate uncomplicated ovarian enlargement, which may be accompanied by abdominal distension and/or abdominal pain, occurs in approximately 5 to 10% of women treated with menotropins and additional hCG for triggering of final follicular maturation, and generally regresses without treatment within two or three weeks. The lowest dose consistent with expectation of good results and careful monitoring of ovarian response can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of MENOPUR therapy, additional hCG for triggering of final follicular maturation should not be administered in this course of treatment; this will reduce the chances of development of the ovarian hyperstimulation syndrome (OHSS).

### Reproductive Health

- **Fertility**

  Multiple pregnancies have occurred following treatment with MENOPUR. In the clinical trial of IVF patients in study 0399E, the rates of multiple pregnancies were as follows: Of the 23 continuing pregnancies, fifteen were single and eight were multiple pregnancies. The eight multiple pregnancies included one triplet and seven twin pregnancies. In the IVF study 2002-02 study, the rates of multiple pregnancies were as follows: Of the thirty continuing pregnancies, thirteen were single and sixteen were multiple pregnancies. The multiple pregnancies included two quadruplet, five triplet and ten twin pregnancies.

  The patient and her partner should be advised of the potential risk of multiple births before starting treatment.

### Respiratory and Cardiovascular

Serious pulmonary conditions (e.g. atelectasis, acute respiratory distress syndrome) have been reported. In addition, thromboembolic events both in association with, and separate from, the OHSS have been reported following menotropins therapy. Intravascular thrombosis and embolism, which may originate in venous or arterial vessels, can result in reduced blood flow to critical organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

### Renal

The safety and efficacy of MENOPUR in renal insufficiency have not been studied.

## 7.1. Special Populations

### 7.1.1. Pregnancy

See 2 Contraindications section.

### 7.1.2. Breastfeeding

See 2 Contraindications section.

### 7.1.3. Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### 7.1.4. Geriatrics

Geriatrics (≥65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

# 8. Adverse Reactions

## 8.1. Adverse Reaction Overview

Sixty-eight percent (67.7%) of patients treated with MENOPUR, compared to 75% of patients treated with the precursor compound REPRONEX, experienced adverse events (AEs). The percentage of patients experiencing AEs following treatment with MENOPUR is similar to the percentage of patients reporting AEs following treatment with recombinant FSH (GONAL-F).

In general, treatment with MENOPUR did not appear to increase the incidence or severity of the expected AEs of abdominal pain, cramps, fullness and enlargement, OHSS, nausea and injection site reactions. Furthermore, adverse events related to local site administration were consistent across the three studies.

In the three studies (0399E, 2000-01 and 2000-02) where pregnancy was a major outcome, there was no difference across treatment groups in the percentage of patients experiencing miscarriage, ectopic pregnancies (all <2%) or elective abortions (all <3%). There also was no notable difference in the percentage of patients with multiple gestations. The number of patients with cycle cancellation due to poor response was small. The most commonly reported serious adverse event was OHSS. The number of patients with OHSS cases considered serious was about 3% in all treatment groups. (see also Overstimulation of the Ovary during MENOPUR Therapy for information on reducing the risk of OHSS)

No remarkable changes in clinical laboratory parameters or physical examination findings / vital signs were observed with MENOPUR treatment in any of the studies in which these parameters were assessed.

The percentage of patients experiencing any AEs or expected AEs did not increase as a function of mean total dose of MENOPUR SC.

## 8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The safety of MENOPUR was examined in 3 clinical studies that enrolled a total of 575 patients receiving MENOPUR in the IVF and ovulation induction (OI) studies. All AEs (without regard to causality assessment) occurring at an incidence of ≥1 % in women treated with MENOPUR undergoing IVF or OI are listed in Table 3 and Table 4.

**Table 3 – MENOPUR subcutaneous (SC) and intramuscular (IM) in female patients undergoing IVF adverse events with onset on and after GnRH administration, COSTART Classification (or incidence of 1% or greater)**

| | **Menotropins for injection IVF * n = 499** | |
|---|---|---|
| **System organ class/preferred term** | **n** | **%** |
| **Body as a whole** | | |
| Headache | 170 | 34 |
| Abdominal Pain | 88 | 18 |
| Injection Site Reaction | 48 | 10 |
| Abdominal Cramps | 30 | 6 |
| Injection Site Pain | 27 | 5 |
| Abdomen Fullness | 16 | 3 |
| Back Pain | 16 | 3 |
| Pain | 16 | 3 |
| Malaise | 14 | 3 |
| Flu Syndrome | 13 | 3 |
| Abdomen Enlarged | 12 | 2 |
| Elevated Estradiol | 12 | 2 |
| Flushing | 12 | 2 |
| Fever | 7 | 1 |
| **Cardiovascular** | | |
| Migraine | 12 | 2 |
| **Digestive** | | |

| | Menotropins for injection<br>IVF *<br>n = 499 | |
|---|---|---|
| Nausea | 60 | 12 |
| Vomiting | 21 | 4 |
| Diarrhea | 14 | 3 |
| Constipation | 8 | 2 |
| **Musculoskeletal** | | |
| Joint disorder | 6 | 1 |
| **Nervous** | | |
| Dizziness | 13 | 3 |
| Emotional lability | 4 | 1 |
| Depression | 3 | 1 |
| **Respiratory** | | |
| Respiratory disorder | 29 | 6 |
| Cough increased | 8 | 2 |
| Pharyngitis | 7 | 1 |
| Sinusitis | 6 | 1 |
| **Skin/Appendages** | | |
| Pruritus | 5 | 1 |
| Rash | 5 | 1 |
| Sweating | 5 | 1 |
| **Urogenital** | | |
| Post retrieval pain | 32 | 6 |
| OHSS | 19 | 4 |
| Vaginal spotting | 18 | 4 |
| Menstrual disorder | 16 | 3 |
| Vaginal hemorrhage | 15 | 3 |
| Breast tenderness | 9 | 2 |
| Uterine spasm | 8 | 2 |
| Ovarian cyst | 7 | 1 |

| | Menotropins for injection IVF * n = 499 | |
|---|---|---|
| Spontaneous abortion | 7 | 1 |
| Urinary tract infection | 7 | 1 |
| Abortion | 5 | 1 |
| Dysmenorrhea | 5 | 1 |
| Ectopic pregnancy | 5 | 1 |
| Breast pain | 4 | 1 |
| Infection fungal | 5 | 1 |
| Vaginal discharge | 5 | 1 |
| Hot flash | 3 | 1 |

* Includes IM and SC subjects from Protocol MFK/IVF/0399E and MENOPUR 2000-02
** Includes IM and SC subjects from Protocol MENOPUR 2000-01

**Table 4 – MENOPUR subcutaneous (SC) and intramuscular (IM) in female patients undergoing and OI adverse events with onset on and after GnRH administration, COSTART Classification (or incidence of 1% or greater)**

| | Menotropins for injection OI ** n = 76 | |
|---|---|---|
| **System organ class/preferred term** | **n** | **%** |
| **Body as a whole** | | |
| Headache | 12 | 16 |
| Injection Site Reaction | 9 | 12 |
| Abdomen Fullness | 7 | 9 |
| Abdominal Pain | 7 | 9 |
| Abdominal Cramps | 5 | 7 |
| Malaise | 2 | 3 |
| Pain | 2 | 3 |
| Flu Syndrome | 1 | 1 |
| **Digestive** | | |
| Nausea | 6 | 8 |

| | Menotropins for injection<br>OI **<br>n = 76 | |
|---|---|---|
| Diarrhea | 2 | 3 |
| Vomiting | 2 | 3 |
| Hemorrhoids | 1 | 1 |
| **Metabolic/Nutritional** | | |
| Peripheral edema | 1 | 1 |
| **Nervous** | | |
| Anxiety | 1 | 1 |
| Depression | 1 | 1 |
| Emotional lability | 1 | 1 |
| **Respiratory** | | |
| Respiratory disorder | 3 | 4 |
| Cough increased | 2 | 3 |
| Nasal Congestion | 1 | 1 |
| Pharyngitis | 1 | 1 |
| Rhinorrhea | 1 | 1 |
| Strep Throat | 1 | 1 |
| **Urogenital** | | |
| OHSS | 10 | 13 |
| Pelvic cramps | 3 | 4 |
| Uterine spasm | 3 | 4 |
| Vaginal hemorrhage | 3 | 4 |
| Breast tenderness | 2 | 3 |
| Hot flash | 2 | 3 |
| Pelvic discomfort | 2 | 3 |
| Vaginal spotting | 2 | 3 |
| Breast pain | 1 | 1 |
| Infection fungal | 1 | 1 |
| Ovarian enlargement | 1 | 1 |

| | Menotropins for injection OI ** n = 76 | |
|---|---|---|
| Persistent chemical pregnancy | 1 | 1 |
| Spontaneous abortion | 1 | 1 |
| Urinary frequency | 1 | 1 |
| Urinary tract infection | 1 | 1 |

* Includes IM and SC subjects from Protocol MFK/IVF/0399E and MENOPUR 2000-02
** Includes IM and SC subjects from Protocol MENOPUR 2000-01

## 8.3. Less Common Clinical Trial Adverse Reactions

The following adverse events occurred in < 1% of the 575 patients treated with MENOPUR:

| | |
|---|---|
| Body as a whole: | ascites, chills and face edema |
| Cardiovascular: | postural hypotension, palpitation and thrombosis |
| Digestive: | decreased appetite, duodenitis, flatulence, gastroenteritis, gingivitis, heartburn, increased appetite, rectal pain, tooth disorder and upset stomach |
| Hemic/lymphatic: | hematoma |
| Metabolic/nutritional: | weight gain |
| Musculoskeletal: | bone pain, leg cramp, muscle pain and twitching |
| Nervous: | sleeps disorder, thinking abnormal and vertigo |
| Respiratory: | bronchitis, dyspnea, epistaxis, hyperventilation, pleural effusion and tonsillitis |
| Special senses: | ear pain, eye disorder, eye pain and taste perversion |
| Urogenital: | abnormal breast, cervical polyp, cystitis, hematuria, dysuria, renal pain, ovarian pain, oliguria, urination impaired, uterine disorder, uterine fibroids, uterine hemorrhage, vaginal and genital erythema, and vaginal and genital swelling |

## 8.5. Post-Market Adverse Reactions

At the time MENOPUR was submitted for initial review in 2004, a total number of 73 adverse events were reported. A total of 41 cases were spontaneously reported, 13 cases from regulatory authorities and 19 cases were serious related cases from clinical trials.

The most frequently reported event was ovarian hyperstimulation syndrome (OHSS), which was reported in 19 cases (2 spontaneously, 1 regulatory report and 16 cases from clinical trials). Two cases of OHSS also included vein thrombosis. OHSS and associated complications, such as thromboembolism, are well-known and related to gonadotropin therapy.

One case of pulmonary embolism without OHSS was reported. According to the literature data, there is a known risk of thromboembolic events without any signs of OHSS related to assisted reproductive technologies.

One case of borderline ovarian cancer was reported. The patient involved was treated with repeated treatment cycles with different gonadotropins and clomiphene citrate, which have been reported as

co-suspected drugs. Several epidemiological studies indicated that ovulation induction drugs might be related to borderline ovarian tumors.

Two events of anaphylaxis and one event of allergic reaction (hypersensitivity) have been reported. Allergic reactions, both local and generalized, are known adverse reactions that might be associated following administration of gonadotropin preparations.

A total of 3 cases described injection site reactions.

## 9. Drug Interactions

### 9.3. Drug-Behaviour Interactions

The interactions of MENOPUR with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

### 9.4. Drug-Drug Interactions

Interactions with other drugs have not been established.

### 9.5. Drug-Food Interactions

Interactions with food have not been established.

### 9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10. Clinical Pharmacology

### 10.1. Mechanism of Action

Menotropins, administered for 7 to 20 days, produce ovarian follicular growth and maturation in women who do not have primary ovarian failure. In order to produce final follicular maturation and ovulation in the absence of an endogenous LH surge, hCG for triggering of final follicular maturation must be administered following menotropins treatment, at a time when patient monitoring indicates sufficient follicular development has occurred.

### 10.2. Pharmacodynamics

Menotropins, which contain both FSH bioactivity and LH bioactivity, induce ovarian follicular growth and development as well as gonadal steroid production in women who do not have primary ovarian failure. FSH bioactivity is the primary driver of follicular recruitment and growth in early folliculogenesis. LH bioactivity, to which LH and hCG contribute, 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 bioactivity in the total absence of LH bioactivity, 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 bioactivity in

enhancing steroidogenesis, oestradiol levels associated with treatment with menotropins 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.

## 10.3. Pharmacokinetics

**Absorption**

The SC route of administration trends greater bioavailability than the IM route for single and multiple doses of menotropins.

**Distribution**

Human tissue or organ distribution of FSH and LH has not been studied for menotropins.

**Metabolism**

Metabolism of FSH and LH has not been studied for menotropins in humans.

**Elimination**

The elimination half-lives for FSH in the multiple-dose phase were the same at 13 hours for menotropins SC and menotropins IM.

Two open-label, randomized, controlled clinical studies were conducted to assess the pharmacokinetics of menotropins. Study 2003-02 (compared single doses of SC administration of the US and European (EU) formulations of menotropins in 57 pituitary-suppressed, healthy, pre-menopausal females. The study established bioequivalence of the two formulations. Study 2000-03 assessed single and multiple doses of menotropins administered SC and IM in a 3 phase cross-over design in 33 pituitary-suppressed, healthy, pre-menopausal females. The primary pharmacokinetic endpoints were FSH AUC and $C_{max}$ values. The results are summarized in Table 5 and

Table **6**.

**Table 5 – Summary of FSH pharmacokinetic parameters in healthy women (Study 2003-02)**

| | $C_{max}$ (mIU/mL | $T_{max}$ (h) | $AUC_{0-120}$ (mIU.h/mL) |
|---|---|---|---|
| **Single Dose SC (400 IU)** | 13.8 + 3.0 | 19.6 + 6.3 | 1040 + 215 |

Mean ±SD shown

**Table 6 -Summary of FSH pharmacokinetic parameters in healthy women (Study 2000-03)**

| | $C_{max}$ (mIU/mL | $T_{max}$ (h) | AUC (mIU.h/mL) |
|---|---|---|---|
| **Single Dose SC (225 IU)** | 8.5 | 17.9 | 726.2 |
| **Single Dose IM (225 IU)** | 7.8 | 26.8 | 656.1 |
| **Multiple Dose SC (225 IU x 1 day then 150 IU x 6 days)** | 15.0 | 8 | 622.7 |
| **Multiple Dose IM (225 IU x 1 day then 150 IU x 6 days)** | 12.5 | 9 | 546.2 |

Single dose AUC120 and multiple dose AUCss

## 11. Storage, Stability, and Disposal

Store lyophilized powder at room temperature (15° to 25°C). Protect from light. Use immediately after reconstitution. Discard unused material.

**Disposal**

The patient should be instructed to safely dispose of all used syringes and needles in a needle disposal container with a lid. Extra sterile diluent should be thrown away. After the patient has completed the course of treatment, she should be instructed on how to properly dispose of the needle disposal container.

## Part 2: Scientific Information

## 13. Pharmaceutical Information

**Drug Substance**

Non-proprietary name of the drug substance(s): Menotropins for injection

Chemical name: Human Menopausal Gonadotropin

Structure: Menotropins contain follicle stimulating hormone (FSH), human chorionic gonadotropin (hCG) and luteinizing hormone (LH)

**Product Characteristics:**

Off-white to yellowish powder, soluble in water up to concentrations of approximately 200 mg/mL. Completely insoluble in ethanol, acetone and ether.

FSH, LH and hCG are glycoproteins that are acidic and water soluble.

Menotropins originate from the urine of postmenopausal women. hCG, a hormone naturally present in the urine of postmenopausal and pregnant women, contributes to the LH bioactivity, and extracted hCG from the urine of pregnant women may be used to balance the total LH bioactivity.

## 14. Clinical Trials

## 14.1. Clinical Trials by Indication

*In vitro* fertilization

**Table 7 – Summary of Patient Demographics for Clinical Trials for in vitro fertilization**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Age (range) | Sex |
|---|---|---|---|---|---|
| IVF Study 0399E | Open-label, active-control, parallel-group, randomized, multi-centre. | MENOPUR SC 75-450 IU QD<br>Follitropin alfa SC 75 -450 IU QD | 727 | 18-38 | Female |
| IVF Study 2000-02 | Open-label, active-control, parallel-group, randomized, multi-centre | MENOPUR SC or IM 75-450 IU QD<br>Menotropins SC 75-450 IU QD | 190 | 18-39 | Female |

| | | | | | |
|---|---|---|---|---|---|
| PK Study 2000-03 | Randomized, open-label, cross-over, parallel group, multi-centre. | Two dosing groups (SC and IM)<br>Three Phases: (I, II, and III) spaced 7 days apart.<br>Phase I and II: Single dose MENOPUR SC or IM 225 IU.<br>Phase I and II: Single dose menotropins 225 IU SC and IM<br>Phase III: Single dose MENOPUR SC or IM 225 IU.<br>225 IU on day 1 followed by 150 IU QD x 6 days | 33 | 18-39 | Female |
| BE Study 2003-02 | Multi-centre, open-label, randomized, single-dose, two period cross-over study. | US MENOPUR SC 400 IU<br>EU MENOPUR SC 400 IU<br>Single dose; two 6-day testing periods each preceded by a 15-28 day pre-treatment period of leuprolide acetate 3.75 mg IM. | 57 | 18- 39 | Female |
| QD = quaque die (once a day) | | | | | |

The efficacy and safety of MENOPUR have been established in two randomized, controlled clinical studies, 0399E and 2000-02, of women undergoing *in vitro fertilization* (IVF) or IVF plus intracytoplasmic injection to achieve pregnancy.

The first trial (IVF Study 0399E) was designed to compare the safety and efficacy of the European formulation of MENOPUR, administered SC, to recombinant FSH (follitropin alfa) in infertile women undergoing an IVF cycle. The second IVF Study 2000-02 compared the safety and efficacy of MENOPUR, administered SC or IM, to the earlier generation version of the product, menotropins, administered SC, in infertile women undergoing an IVF cycle.

**Study Results**

*Study 0339E*

Study 0399E was a Phase III, randomized, open-label, multicenter, multinational (in Europe and Israel), comparative clinical trial of ovulatory, infertile females undergoing ovarian stimulation to produce multiple follicles for IVF and embryo transfer (IVF/ET) after pituitary suppression with a GnRH agonist. A total of 727 patients were enrolled. Three hundred seventy three (373) patients were randomized to the MENOPUR arm and three hundred fifty four (354) were randomized to the follitropin alfa arm. Randomization was stratified by insemination technique [conventional in-vitro fertilization (IVF) vs. intra-cytoplasmic sperm injection (ICSI)]. Efficacy was assessed based on the primary efficacy parameter of continuing pregnancy. The initial daily dose of MENOPUR was 225 IU SC for five days. Thereafter, the dose was individualized according to each patient's response, up to a maximum of 450 IU/day for a total maximum duration of stimulation of 20 days. Treatment outcomes are summarized in Table 8.

**Table 8: Efficacy Outcomes for IVF Study 0399E (one cycle of treatment)**

| Parameter | MENOPUR SC n=373 | follitropin alfa SC n=354 |
|---|---|---|
| Average Number of Days of Stimulation | 11.5 | 11.5 |
| Mean Number of Vials/Ampoules Used | 37 | 37 |
| Mean Peak Serum $E_2$ (pg/mL) | 2213 | 1700 |
| Mean Total Oocytes Retrieved Per Patient | 13 | 14 |
| Oocyte Retrieval (%) | 361 (97) | 339 (96) |
| Embryo Transfer (%) | 336 (90) | 316 (89) |
| Chemical Pregnancy (%) | 119 (32) | 101(29) |
| Clinical Pregnancy (%) | 98 (26) | 78 (22) |
| Continuing Pregnancy (%) | 87(23) | 73 (20) |

$E_2$ = estradiol

In the IVF study 0399E, MENOPUR was non-inferior to follitropin alfa in terms of percentage of patients with an ongoing pregnancy in the treatment of women undergoing IVF/ICSI. This was true for both the Intent-To-Treat (ITT) population and the Per Protocol (PP) population.

**Table 9 – Results of Primary Efficacy Parameter in Subjects with Ongoing Pregnancy – Intent to Treat IVF Study 0399E**

| | Study 0399E | | | | |
|---|---|---|---|---|---|
| **Parameter** | **MENOPUR n = 373** | | **follitropin alfa n = 354** | | **unadjusted[a] treatment difference (95% CI)** |
| | No. | % | No. | % | |
| Ongoing Pregnancy | 87 | 23.3 | 73 | 20.6 | -3.3, 8.7[b] |

a. Based on normal approximation (unadjusted)

b. Statistically not significant for MENOPUR vs follitropin alfa comparison (p = 0.42)

**Table 10 – Results of Primary Efficacy Parameter in Subjects with Ongoing Pregnancy – Per Protocol IVF Study 0399E**

| | Study 0399E | | | | |
|---|---|---|---|---|---|
| **Parameter** | **MENOPUR n = 357** | | **follitropin alfa n = 336** | | **unadjusted [a] treatment difference (95% CI)** |
| | No. | % | No. | % | |
| Ongoing Pregnancy | 85 | 23.8 | 71 | 21.1 | -3.5, 7.9[b] |

a. Based on normal approximation (unadjusted)

b. Statistically not significant for MENOPUR vs follitropin alfa comparison (p = 0.41)

*Study 2000-02*

Study 2000-02 was an open label, parallel group, randomized study in women undergoing in vitro fertilization. A total of 190 patients were randomized, of whom 126 received MENOPUR (MENOPUR SC n=61 and MENOPUR IM n=65). All patients received luteal phase GnRH agonist pituitary suppression and underwent controlled ovarian stimulation at an initial daily dose of 225 IU for five days. Thereafter, the dose was individualized according to each patient's response, up to a maximum of 450 IU/day for a total maximum duration of stimulation of 12 days. When transvaginal ultrasound showed ≥3 follicles of diameter ≥16 mm with a clinically appropriate serum $E_2$ level, hCG for triggering of final follicular maturation was administered (10,000 IU) and oocytes were retrieved approximately 36 hours later. One to four embryos were transferred.

The primary efficacy outcome was the total number of oocytes retrieved following the administration of hCG for triggering of final follicular maturation. Treatment outcomes are summarized in Table 11.

| Table 11: Efficacy Outcome for IVF Study 2000-02 (one cycle of treatment) | |
|---|---|
| **Parameter** | **MENOPUR SC n = 61** |
| Average Number of Days of Stimulation | 9.6 |
| Mean Number of Vials/Ampoules Used | 35 |
| Mean Peak Serum $E_2$ (pg/mL) | 2007 |
| Mean Total Oocytes Retrieved Per Patient | 13 |
| Mean Mature Oocytes Retrieved Per Patient | 10 |
| Oocyte Retrieval (%) | 61 (100) |
| Embryo Transfer (%) | 57 (93) |
| Chemical Pregnancy (%) | 24 (39) |
| Clinical Pregnancy (%) | 18 (30) |
| Continuing Pregnancy (%) | 18 (30) |
| Patients with Live Births (%) | 12 (20) |

Calculated from mean total dose/75 IU (MENOPUR SC=2625/75 IU)

In the IVF study 2000-02, MENOPUR in terms of the primary efficacy parameter – the number of oocytes retrieved per cycle (patient), showed no statistically significant differences to menotropins SC in either the ITT or primary efficacy responder (received hCG for triggering of final follicular maturation) population as shown below.

| Table 12 Primary Efficacy Parameter: Number Oocytes Retrieved – Intent to Treat IVF Study 2000-02 | | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **MENOPUR SC N = 61** | | **menotropins SC N = 64** | | **95 % CI** | **p-value** |
| | **Mean** | **SD** | **Mean** | **SD** | | |
| Number of oocytes retrieved | 13.1 | ± 7.2 | 14.4 | ± 7.7 | -4.0 | 0.341 |
| Number of mature oocytes retrieved | 9.9 | ± 4.8 | 10.9 | ± 7.0 | | 0.621 |

| Table 13 Primary Efficacy Parameter: Number Oocytes Retrieved Primary Efficacy Responders (Received additional hCG) IVF Study 2000-02 | | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **MENOPUR SC N = 61** | | **menotropins SC N = 62** | | **95 % CI** | **p-value** |
| | **Mean** | **SD** | **Mean** | **SD** | | |
| Number of oocytes retrieved | 13.1 | ± 7.2 | 14.9 | ± 7.4 | -4.3 | 0.188 |
| Number of mature oocytes retrieved | 9.9 | ± 4.8 | 11.2 | ± 6.8 | | 0.209 |

*Comparisons between Studies 0330E and 2000-02*

A comparison in terms of the numbers of oocytes retrieved in the IVF studies 0399E and 2000-02 between MENOPUR SC and REPRONEX SC is shown in Table 14.

**Table 14**

| **Table 14<br>Mean Number of Oocytes Retrieved<br>Intent to Treat** | | | |
|---|---|---|---|
| Controlled Study | MENOPUR SC<br>n=61 | menotropins SC<br>n=64 | p-value |
| IVF Study 2000-02 | 13.1 | 14.4 | 0.341 |
| | n=373 | follitropin alfa SC<br>n=354 | |
| IVF Study 0399E | 12.4 | 13.4 | 0.126[1] |

[1] From t-test

Comparisons in terms of the percentage of patients (cycles) with chemical, clinical and continuing pregnancies in the IVF studies 0399E and 2000-02, between MENOPUR SC and menotropins SC are shown in Table 15, Table 16, and Table 17.

| **Table 15<br>Patients with Chemical[1] Pregnancy<br>Intent to Treat** | | | | | | |
|---|---|---|---|---|---|---|
| Controlled Study | n | MENOPUR SC | | menotropins SC | | p-value[2] |
| | | No. | % | No. | % | |
| IVF Study 2000-02 | 190 | 24 | 39.3 | 32 | 50 | 0.231 |
| | | | | follitropin alfa SC | | |
| IVF Study 0399E | 727 | 119 | 31.9 | 101 | 28.5 | 0.320 |

[1] Positive serum βhCG

[2] From between groups ANOVA for studies 2000-01 and -02, and from Chi-Square test for MKF/IVF/0399E

| **Table 16<br>Patients with Clinical[1] Pregnancy<br>Intent to Treat** | | | | | | |
|---|---|---|---|---|---|---|
| Controlled Study | n | MENOPUR SC | | menotropins SC | | p-value[2] |
| | | No. | % | No. | % | |
| IVF Study 2000-02 | 190 | 18 | 29.5 | 26 | 40.6 | 0.193 |
| | | | | follitropin alfa SC | | |
| IVF Study 0399E | 727 | 98 | 26.3 | 78 | 22.0 | 0.190 |

[1] Ultrasound showing intrauterine sac

[2] From between groups ANOVA for studies 2000-01 and -02, and from Chi-Square test for MKF/IVF/0399E

| Table 17<br>Patients with Continuing[1] Pregnancy<br>Intent to Treat | | | | | | |
|---|---|---|---|---|---|---|
| Controlled Study | n | MENOPUR SC | | menotropins SC | | p-value[2] |
| | | No. | % | No. | % | |
| IVF Study 2000-02 | 190 | 18 | 29.5 | 24 | 37.5 | 0.344 |
| | | | | follitropin alfa SC | | |
| IVF Study 0399E | 727 | 87 | 23.3 | 73 | 20.6 | 0.42 |

[1] Ultrasound showing intrauterine sac and fetal heart motion

[2] From between groups ANOVA for studies 2000-01 and -02, and from Chi-Square test for MKF/IVF/0399E

A comparison between MENOPUR, REPRONEX and GONAL-F with respect to the major secondary endpoint of serum estradiol level is illustrated in Table 18.

| Table 18<br>Mean Peak Serum $E_2$ Levels pg/mL<br>(Intent to Treat Population) | | | | | | |
|---|---|---|---|---|---|---|
| Controlled Study | n | MENOPUR SC | | menotropins SC | | p-value[1] |
| | | Mean | SD | Mean | SD | |
| Purified menotropins 2000-02 | 190 | 2007.1 | 1008.3 | 2462.8 | 1483.1 | 0.053 |
| | | | | follitropin alfa SC | | |
| MFK/IVF/0399E | 679[2] | 2213.0[3] | 1614.5 | 1700.0 | 1203.8 | 0.001 |

[1] For the US study, from one-way ANOVA. For the multinational study, from Wilcoxon Rank Sum Test

[2] Forty-eight patients from the ITT population did not have estradiol data available on the day of hCG administration for triggering of final follicular maturation; therefore the n was reduced to 679

[3] A conversion factor of 3.671 was used to convert pmol/mL to pg/mL

The number of days of stimulation required to reach additional hCG administration criteria and total dose of gonadotropin administered in the IVF studies 0399E and 2000-02 between MENOPUR SC and menotropins SC are presented in Table 19 and Table 20.

| Table 19<br>Number of Days to Meet Additional hCG Administration Criteria | | | | | | |
|---|---|---|---|---|---|---|
| Controlled Study | n | MENOPUR SC | | menotropins SC | | p-value[1] |
| | | Mean | SD | Mean | SD | |
| Purified menotropins 2000-02 | 190 | 9.60 | 1.40 | 9.4 | 1.40 | 0.356 |
| | | | | follitropin alfa SC | | |
| MFK/IVF/0399E | 727 | 11.54 | 1.91 | 11.52 | 2.00 | 0.860 |

[1] From one-way ANOVA

| Table 20<br>Average Total Dose of Gonadotropin | | | | | | |
|---|---|---|---|---|---|---|
| Controlled Study | n | MENOPUR SC | | menotropins SC | | p-value[1] |
| | | Mean | SD | Mean | SD | |
| Purified menotropins 2000-02 | 190 | 2625.0 | 847.7 | 2463.3 | 831.3 | 0.297 |
| | | | | follitropin alfa SC | | |
| MFK/IVF/0399E | 727 | 2767.5[2] | --- | 2775.0[3] | --- | 0.850 |

[1] For the US studies, from one-way ANOVA. For the multinational study, from Wilcoxon Rank Sum Test
[2] Calculated from mean number of vials/ampoules used - 36.0 x 75 IU/vial
[3] Calculated from mean number of vials/ampoules used - 37.0 x 75 IU/vial

## 14.2. Comparative Bioavailability Studies

*Study 2003-02*

Study 2003-02 was conducted to assess bioequivalence between the US and EU MENOPUR formulation after subcutaneous injection in female subjects. The data from this study demonstrated that the pharmacokinetic profile of US MENOPUR was similar to that of EU MENOPUR. The mean serum FSH parameters from the 52 subjects ($C_{max}$, $AUC_{0-120}$ and $T_{max}$) after subcutaneous administration of the US MENOPUR and EU MENOPUR are presented in Table 21 below.

**Table 21– Summary Table of the Comparative Bioavailability Data (Study 2003-02)**

| Baseline-corrected serum FSH<br>(MENOPUR US vs MENOPUR EU)<br>Least squares means ±SD | | | | |
|---|---|---|---|---|
| **Parameter** | **Test[1]** | **Reference[2]** | **% Ratio of least squares means** | **90% Confidence Interval** |
| $AUC_{0-120}$ (mIU•h/mL) | 651.65 ± 182.89 | 675.70 ± 162.53 | 96.4% | 84.9 – 109.5% |
| $C_{MAX}$ (mIU/mL) | 10.59± 3.07 | 11.43 ± 2.31 | 92.7% | 83.2 -103.3% |
| $T_{MAX}$ (h) | 19.32±6.27 | 18.85± 6.96 | | 86.5 – 118.4% |

[1] MENOPUR US, menotropins, subcutaneous injection, 75 IU/VIAL, FDA.
[2] MENOPUR EU, menotropin, subcutaneous injection, 75 IU/VIAL, EMA

## 16. Non-Clinical Toxicology

No long-term animal studies have been performed to evaluate the carcinogenic or mutagenic potential or whether menotropins for injection affects fertility in males or females.

## Patient Medication Information

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**[Pr]MENOPUR®**

**Menotropins for Injection**

This Patient Medication Information is written for the person who will be taking **MENOPUR**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **MENOPUR**, talk to a healthcare professional.

**What MENOPUR is used for:**

The active ingredient in MENOPUR is known as menotropins. Menotropins contain follicle stimulating hormone (FSH), luteinizing hormone (LH), and human chorionic gonadotropin (hCG). FSH, LH and hCG in MENOPUR are obtained from the urine of women who have gone through menopause and women who are pregnant. FSH, LH and hCG are natural hormones produced in women. They help the reproductive organs to work normally.

Your doctor may have prescribed MENOPUR because your pituitary gland does not release FSH, or it releases FSH and LH in an improper balance. This imbalance means the follicles are unable to mature, so ovulation cannot take place. MENOPUR helps to provide the required amount of FSH to the ovaries, thereby allowing the ovarian follicles to develop.

MENOPUR is used in IVF (in-vitro fertilization or “test tube”) procedures or other assisted conception techniques to induce multiple follicular development.

**How MENOPUR works:**

MENOPUR provides you with the FSH that is necessary for the recruitment, growth and maturation of the ovarian follicles which contain eggs known as ova. This occurs at the beginning of the cycle. After MENOPUR is given to develop the ovarian follicle, additional hCG is given mid cycle to mature the egg and induce ovulation.

**Length of one treatment cycle:** The length of treatment depends on the average follicular response to therapy. Every cycle treatment is individualized and your doctor will need to carefully evaluate how you respond.

**The ingredients in MENOPUR are:**

Medicinal ingredients: Menotropins – FSH, LH and hCG

Non-medicinal ingredients: lactose monohydrate, polysorbate 20, sodium phosphate, and phosphoric buffer (sodium phosphate dibasic, heptahydrate and phosphoric acid)

**MENOPUR comes in the following dosage form(s):**

Sterile lyophilized powder, 75 IU / vial (75 IU FSH bioactivity/ 75 IU LH bioactivity)

**Do not use MENOPUR if:**

- You are pregnant
- You are breast-feeding

**MENOPUR should also not be used if you have:**

- A high level of FSH indicating primary ovarian failure.
- Uncontrolled thyroid or adrenal dysfunction.
- An organic intracranial lesion such as pituitary tumour.
- Abnormal vaginal bleeding of undetermined origin.
- Ovarian cyst or enlargement not due to polycystic ovarian syndrome (PCOS).
- Allergy to menotropins, lactose monohydrate, polysorbate 20, sodium phosphate buffer (sodium phosphate dibasic, heptahydrate and phosphoric acid).
- Tumour of the ovaries, fallopian tubes, uterus, vagina, breast and cervix.

MENOPUR should only be used under the supervision a specialist having the required facilities for laboratory monitoring.

**Other warnings you should know about:**

**Risk of reproductive complications associated with MENOPUR:** Treatment with gonadotropin preparations may lead to unwanted overstimulation of the ovaries known as ovarian hyperstimulation syndrome (OHSS). The first symptoms of ovarian stimulation may be noticed as pain in the abdomen, feeling sick or diarrhea. More severe cases may have accumulation of fluid in the abdomen and/or chest, weight gain and the occurrence of blood clots. Contact your doctor without delay if you experience any of these symptoms during treatment or within a few days after the last injection.

The incidence of multiple births with MENOPUR is no different from any other gonadotropin and is dependent upon the protocol used by the clinic. Your doctor will monitor you closely to help minimize the possibility of multiple gestations. The majority of births – about 85% are single babies. Of those women who have multiple births, the majority of these are twins. Only few women conceive 3 or more babies. Even so, neither single nor multiple births can be totally guaranteed.

Since women with infertility undergoing infertility assisted reproduction, and particularly IVF, often have tubal abnormalities, the incidence of ectopic pregnancies may be increased. Early ultrasound confirmation of pregnancy in the uterus is therefore of importance.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**How to take MENOPUR:**

MENOPUR must be taken by injection.

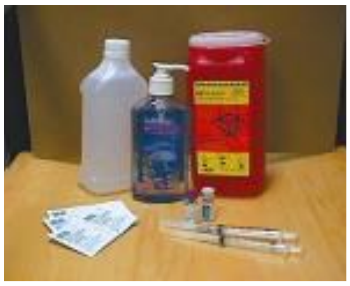
Every treatment is individualized. Yours has been carefully designed for you by your doctor according to your own specific needs. It is very important that you keep your appointments and follow your doctor's instructions, particularly with regard to the amount and frequency of the medication you are taking. If you have concerns regarding your dosage, consult your doctor. Do not adjust your dosage without being instructed to do so. If you forget or miss an injection, stay calm, and call your doctor for advice.

***Instructions for Reconstitution and Subcutaneous Administration***

Your doctor has prescribed MENOPUR for subcutaneous injection. This means that it is injected through a short injection needle into the tissue just under your skin. This instruction sheet will help you prepare and inject your medication at home. Please review it completely prior to starting the procedure.

Do not attempt this procedure if you are unsure of how to prepare or administer the injection. If you have any questions, call your doctor or nurse.

**1) Before You Start**

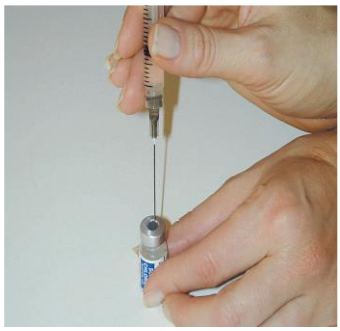


- Wash your hands with antibacterial soap and use alcohol to clean the area you will be working on.
- Have these supplies ready:
  - Vial (or vials) of MENOPUR, 75 IU
  - A vial of 0.9% Sodium Chloride (sterile diluent). If you have the kit, the diluent is conveniently packaged with MENOPUR
  - A syringe and sterile needles (check with your doctor about which syringe and needle size to use)
  - Alcohol pads and rubbing alcohol
  - Gauze and cotton balls
  - A needle disposal container

**2) Preparing your medicine and filing the syringe**

Remember: *Only 0.9% Sodium Chloride injection, USP (sterile diluent) must be used to reconstitute MENOPUR.*

- Remove syringe and larger needle from the wrapper. While holding the protective cap, twist needle clockwise to make sure needle is secure. Set syringe and needle aside.
- Remove plastic caps from tops of vials of MENOPUR and sterile diluent.

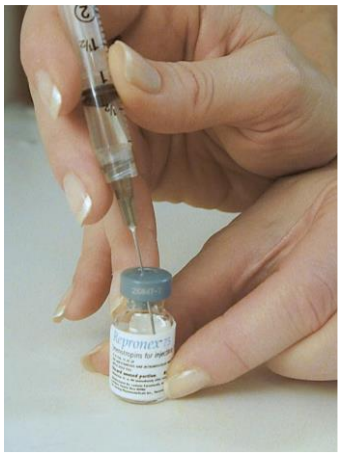


- Wipe tops of vials with alcohol to sterilize them. Don't touch tops of vials once you have sterilized them.
- Uncap needle by carefully twisting needle cap clockwise and pulling cap upward. Avoid twisting needle counterclockwise, as this can cause needle to separate from syringe.
- Insert needle through rubber stopper of sterile diluent vials.
- Tip sterile diluent vial and, with needle in fluid, pull back on plunger to withdraw fluid into syringe up to the amount instructed by your doctor.
- Withdraw needle from sterile diluent vial. Slowly inject sterile diluent into vial containing MENOPUR powder, aiming sterile diluent at side of vial to avoid creating bubbles. The solution should be clear and colourless.

**The MENOPUR powder will dissolve quickly. Do not shake vial because this will create bubbles.**

**For patients requiring a single injection from multiple vials of MENOPUR, up to 6 vials can be reconstituted with 1 mL of 0.9% sodium chloride injection, USP.**

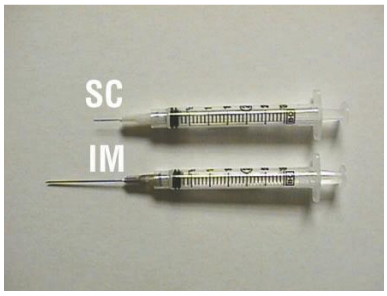
This can be accomplished by reconstituting a single vial as described above (see step 2). Then draw the entire contents of the first vial into a syringe, and inject the contents into a second vial of lyophilized MENOPUR. Gently swirl the second vial as described above, once again checking to make sure the solution is clear and free of particles. This step can be repeated with 4 additional vials for a total of up to 6 vials of lyophilized MENOPUR into 1 mL of diluent.



- As soon as powder has completely dissolved, withdraw all MENOPUR solution into syringe. There are two ways of doing this:

  A. Leave vial on counter, tilt it, pull back on plunger to withdraw all solution, **OR**
  B. Turn vial upside down, pull back on plunger to withdraw solution as you slowly lower needle.

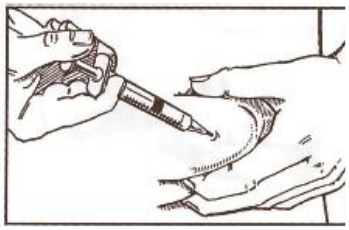
**3) Changing the Needle**

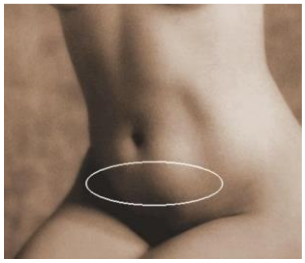



- While holding syringe upward, replace needle cap and remove large needle by twisting it counterclockwise. Replace with the small, subcutaneous needle by twisting it clockwise onto syringe.
- Hold syringe straight up. Draw back slightly on plunger and tap syringe so that *any* air bubbles rise to top. Slowly press plunger until all air is out of syringe and small drop of solution forms at tip of needle.
- Tap the syringe to remove the drop of solution at the tip of the needle.
- Carefully recap needle to keep it sterile.
- MENOPUR solution is now ready for injection.

If an uncapped needle EVER comes into contact with anything except MENOPUR or sterile diluent, do not inject yourself with it. Immediately remove needle and replace it with a new sterile needle.

**4) Injecting the Medicine**





MENOPUR should be injected into a skin fold on your abdomen a few inches below your navel, to the left or right.

Each day, use the alternate side of your abdomen to help prevent soreness.

- Carefully clean injection site area with an alcohol pad and allow site to air-dry.
- Remove needle cap from syringe.
- Hold syringe in one hand. Use your other hand to gently grasp a fold of skin in the injection site area between your thumb and index finger.
- Hold syringe perpendicular (at right angle) to skin like a dart and quickly insert needle all the way into skin fold.
- Depress plunger of syringe with a steady motion until all fluid is injected beneath skin.
- Release skin fold and pull needle straight out. Recap needle and discard syringe and needle into a disposal container. If any bleeding should occur, simply place a small piece of gauze or cotton over the injection site and apply gentle pressure to stop bleeding.
- If injection site becomes sore, application of ice for brief intervals may help relieve any discomfort.

**5) Disposal of the Syringe and Needles**


Safely dispose of all used syringes and needles in a needle disposal container with a lid. Extra sterile diluent should be thrown away. After you finish your course of treatment, ask your healthcare professional how to properly dispose of the needle disposal container.

**Usual dose:**

The dose is chosen by your doctor. Women participating in assisted reproduction programs are usually started on a dose of 225 IU MENOPUR. Based on clinical monitoring including ovarian ultrasound scans, and blood and urine tests, you doctor may adjust the dose once every two days. The maximum daily dose of MENOPUR is 450 IU daily.

**Overdose:**

If you think you, or a person you are caring for, have taken too much MENOPUR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

**Missed dose:**

If the patient misses a dose, the patient should be advised to take the missed dose and not to double dose.

**Possible side effects from using MENOPUR:**

These are not all the possible side effects you may have when taking MENOPUR. If you experience any side effects not listed here, tell your healthcare professional.

Fertility drugs are safe to take with close monitoring by your doctor. As with all medications, there is a potential for side effects. Some patients undergoing gonadotropin therapy may experience breast tenderness, bloating, flushing, vomiting, nausea and diarrhea. They are temporary and will resolve once treatment is stopped. Other adverse reactions may include allergic sensitivity such as a rash or local swelling at the injection site.

The greatest concern your doctor will have is ovarian hyperstimulation syndrome (OHSS). To avoid the development of OHSS, your doctor will carefully monitor your response to MENOPUR. Ovarian enlargement, sometimes accompanied by abdominal bloating and pain, may occur in about 20% of women taking gonadotropins. This is generally reversed with cessation of treatment and severe life-threatening cases are rare.

A causal relationship between treatment of fertility drugs and ovarian cancer has not been established.

If you experience any unusual symptoms or side effects, you should report them to your doctor immediately. It is also wise to discuss the possibility of side effects with your doctor before your treatment.

**Serious side effects and what to do about them**

| Frequency/Side Effect/Symptom | Talk to your healthcare professional | | Stop taking this drug and get immediate medical help |
|---|---|---|---|
| | Only if severe | In all cases | |
| **Common** | | | |
| Mild OHSS | | ✓ | ✓ |
| **Rare** | | | |
| Severe OHSS | | ✓ | ✓ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting side effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Store MENOPUR at room temperature (15° to 25°C). Protect from light. Use immediately after reconstitution. Discard unused material.

Keep out of reach and sight of children.

**If you want more information about MENOPUR:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); Ferring Inc.'s website: www.ferring.ca, or by calling 1-866-384-1314.

This leaflet was prepared by Ferring Inc.

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