# PRODUCT MONOGRAPH

# PrMENOPUR®

Menotropins for Injection, USP
(Powder for Solution)

For SC Use Only

75 IU/ Vial

(75 IU FSH/ 75 IU LH)

GONADOTROPINS FOR INFERTILITY

FERRING INC.
200 Yorkland Boulevard, Suite 800
North York, Ontario
M2J 5C1

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**TABLE OF CONTENTS**

**MENOPUR®**

Menotropins for Injection USP

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY OF PRODUCT INFORMATION

| Route of Administration | Dosage Form/Strength | Clinically Relevant Non-medicinal Ingredients |
|---|---|---|
| Subcutaneous (SC) injection | Lyophilized powder for reconstitution and injection | Lactose Monohydrate; Polysorbate 20, Sodium Phosphate Buffer (Sodium Phosphate Dibasic, Heptahydrate and Phosphoric Acid). |

### DESCRIPTION

Menopur® (menotropins for injection, USP) is a preparation of gonadotropins, extracted from the urine of postmenopausal women, which has undergone additional steps for purification. Each vial of Menopur® contains 75 International Units (IU) of Follicle Stimulating Hormone (FSH) activity and 75 IU of Luteinizing Hormone (LH) activity, plus 21 mg Lactose Monohydrate and 0.005 mg, Polysorbate 20 and Sodium Phosphate Buffer (Sodium Phosphate Dibasic, Heptahydrate and Phosphoric Acid) in a sterile, lyophilized form intended for reconstitution with sterile 0.9% Sodium Chloride Injection, USP.

Menopur® is administered by subcutaneous (SC) injection. Human Chorionic Gonadotropin (hCG), a naturally occurring hormone in postmenopausal urine, is present in Menopur® and contributes to the overall luteinizing hormone activity.

Both FSH and LH are glycoproteins that are acidic and water soluble.

## INDICATIONS AND CLINICAL USE

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

1. 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 IVF program.
2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.
3. Careful examination should be made to rule out the presence of an early pregnancy.
4. Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory 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.
5. Evaluation of the partner's fertility potential should be included in the work-up.

### Geriatric Populations

Menopur® is not used in geriatric populations.

### Pediatric Populations

Menopur® is not used in pediatric populations.

## CONTRAINDICATIONS

Menopur® is contraindicated in women who have:

1. A high FSH (Follicle Stimulating Hormone) level indicating primary ovarian failure.
2. Uncontrolled thyroid or adrenal dysfunction.
3. An organic intracranial lesion such as a pituitary tumour.
4. Abnormal vaginal bleeding of undetermined origin.
5. Ovarian cysts or enlargement not due to Polycystic Ovarian Syndrome.

6. Prior hypersensitivity to menotropins or Menopur® or to any ingredient in the formulation or component of the container. For complete list, see dosage forms, composition and packaging section of the product monograph.
7. Menopur® is not indicated in women who are pregnant. There are limited human data on the effects of menotropins when administered during pregnancy.
8. Sex hormone dependent tumours of reproductive tract and accessory organs.

## WARNINGS AND PRECAUTIONS

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 **WARNINGS AND PRECAUTIONS Laboratory Tests**).

### Overstimulation of the Ovary during Menopur® Therapy

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 hCG, 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, hCG should not be administered in this course of treatment; this will reduce the chances of development of the Ovarian Hyperstimulation Syndrome (OHSS).

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 **Pulmonary and Vascular Complications**). 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. 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 hCG administration (see **Laboratory Tests**), the hCG 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.

**Pulmonary and Vascular Complications**

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.

**Multiple Pregnancies**

Multiple pregnancies have occurred following treatment with Menopur® SC. 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.

**General**

Careful attention should be given to the diagnosis of infertility in the selection of candidates for Menopur® therapy (see **INDICATIONS AND CLINICAL USE- 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 **ADVERSE REACTIONS**) and the risk of multiple births should also be discussed.

**Laboratory Tests**

The combination of both estradiol levels and ultrasonography are useful for monitoring the growth and development of follicles, timing of hCG administration, 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.

**Carcinogenesis and Mutagenesis**

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

**Renal and Hepatic Insufficiency**

The safety and efficacy of Menopur® in renal and hepatic insufficiency have 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.

**Special Populations**

**Pregnancy**

See **CONTRAINDICATIONS** section.

**Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if menotropins are administered to a nursing woman.

**Pediatric Patients**

Menopur is not used in pediatric populations.

**Geriatric Populations**

Menopur® is not used in geriatric populations.

## ADVERSE REACTIONS

### Adverse Drug Reactions 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, within each study, Menopur® was found to be well-tolerated locally.

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.

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.

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related AEs and for approximating rates.*

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

| TABLE 1: MENOPUR ® SC AND IM IN FEMALE PATIENTS UNDERGOING IVF AND OI ADVERSE EVENTS WITH ONSET ON AND AFTER GNRH ADMINISTRATION, COSTART CLASSIFICATION (FOR INCIDENCE OF 1% OR GREATER) | | | | |
|---|---|---|---|---|
| | IVF * N = 499 | | OI ** N = 76 | |
| **BODY SYSTEMS/PREFERRED TERM** | **N** | **%** | **N** | **%** |
| | | | | |
| **BODY AS A WHOLE** | | | | |
| Abdomen Enlarged | 12 | 2.4 | 0 | 0.0 |
| Abdominal Cramps | 30 | 6.0 | 5 | 6.6 |
| Abdomen Fullness | 16 | 3.2 | 7 | 9.2 |
| Abdominal Pain | 88 | 17.6 | 7 | 9.2 |
| Back Pain | 16 | 3.2 | 0 | 0.0 |
| Elevated Estradiol | 12 | 2.4 | 0 | 0.0 |
| Fever | 7 | 1.4 | 0 | 0.0 |
| Flu Syndrome | 13 | 2.6 | 1 | 1.3 |
| Flushing | 12 | 2.4 | 0 | 0.0 |
| Headache | 170 | 34.1 | 12 | 15.8 |
| Injection Site Pain | 27 | 5.4 | 0 | 0.0 |
| Injection Site Reaction | 48 | 9.6 | 9 | 11.8 |
| Malaise | 14 | 2.8 | 2 | 2.6 |
| Pain | 16 | 3.2 | 2 | 2.6 |
| **CARDIOVASCULAR** | | | | |
| Migraine | 12 | 2.4 | 0 | 0.0 |
| **DIGESTIVE** | | | | |
| Constipation | 8 | 1.6 | 0 | 0.0 |
| Diarrhea | 14 | 2.8 | 2 | 2.6 |
| Hemorrhoids | 0 | 0.0 | 1 | 1.3 |
| Nausea | 60 | 12.0 | 6 | 7.9 |
| Vomiting | 21 | 4.2 | 2 | 2.6 |
| **METABOLIC/NUTRITIONAL** | | | | |
| Peripheral edema | 0 | 0.0 | 1 | 1.3 |
| **MUSCULOSKELETAL** | | | | |
| Joint disorder | 6 | 1.2 | 0 | 0.0 |
| **NERVOUS** | | | | |
| Anxiety | 1 | 0.2 | 1 | 1.3 |
| Depression | 3 | 0.6 | 1 | 1.3 |
| Dizziness | 13 | 2.6 | 0 | 0.0 |
| Emotional lability | 4 | 0.8 | 1 | 1.3 |

| TABLE 1: MENOPUR ® SC AND IM IN FEMALE PATIENTS UNDERGOING IVF AND OI ADVERSE EVENTS WITH ONSET ON AND AFTER GNRH ADMINISTRATION, COSTART CLASSIFICATION (FOR INCIDENCE OF 1% OR GREATER) | | | | |
|---|---|---|---|---|
| | IVF * N = 499 | | OI ** N = 76 | |
| BODY SYSTEMS/PREFERRED TERM | N | % | N | % |
| RESPIRATORY | | | | |
| Cough increased | 8 | 1.6 | 2 | 2.6 |
| Nasal Congestion | 1 | 0.2 | 1 | 1.3 |
| Pharyngitis | 7 | 1.4 | 1 | 1.3 |
| Respiratory disorder | 29 | 5.8 | 3 | 3.9 |
| Rhinorrhea | 0 | 0.0 | 1 | 1.3 |
| Sinusitis | 6 | 1.2 | 0 | 0.0 |
| Strep Throat | 0 | 0.0 | 1 | 1.3 |
| SKIN/APPENDAGES | | | | |
| Puritus | 5 | 1.0 | 0 | 0.0 |
| Rash | 5 | 1.0 | 0 | 0.0 |
| Sweating | 5 | 1.0 | 0 | 0.0 |
| UROGENITAL | | | | |
| Abortion | 5 | 1.0 | 0 | 0.0 |
| Breast pain | 4 | 0.8 | 1 | 1.3 |
| Breast tenderness | 9 | 1.8 | 2 | 2.6 |
| Dysmenorrhea | 5 | 1.0 | 0 | 0.0 |
| Ectopic pregnancy | 5 | 1.0 | 0 | 0.0 |
| Hot flash | 3 | 0.6 | 2 | 2.6 |
| Infection fungal | 5 | 1.0 | 1 | 1.3 |
| Menstrual disorder | 16 | 3.2 | 0 | 0.0 |
| OHSS | 19 | 3.8 | 10 | 13.2 |
| Ovarian cyst | 7 | 1.4 | 0 | 0.0 |
| Ovarian enlargement | 0 | 0.0 | 1 | 1.3 |
| Pelvic cramps | 0 | 0.0 | 3 | 3.9 |
| Pelvic discomfort | 2 | 0.4 | 2 | 2.6 |
| Persistent chemical pregnancy | 0 | 0.0 | 1 | 1.3 |
| Post retrieval pain | 32 | 6.4 | 0 | 0.0 |
| Spontaneous abortion | 7 | 1.4 | 1 | 1.3 |
| Urinary frequency | 0 | 0.0 | 1 | 1.3 |
| Urinary tract infection | 7 | 1.4 | 1 | 1.3 |
| Uterine spasm | 8 | 1.6 | 3 | 3.9 |
| Vaginal discharge | 5 | 1.0 | 0 | 0.0 |
| Vaginal hemorrhage | 15 | 3.0 | 3 | 3.9 |
| Vaginal spotting | 18 | 3.6 | 2 | 2.6 |

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

** Includes IM and SC subjects from Protocol Menopur 2000-01

**Less Common Clinical Trials Adverse Drug reaction (< 1%)**

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/LYMPATIC: | 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 erythemia, and vaginal and genital swelling |

**Post-Market Adverse Drug Reactions**

Since the first approval of Menopur® in 1999, a total number of 73 adverse events have been 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, suggesting good local tolerability of Menopur®.

## DRUG INTERACTIONS

No drug/drug interaction studies have been conducted for Menopur® in humans.

### Drug Abuse and Dependence

There have been no reports of abuse or dependence with menotropins.

## DOSAGE AND ADMINISTRATION

### 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.

## 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, hCG (5000 – 10,000 USP units) should be administered to induce final follicular maturation in preparation for oocyte retrieval. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of therapy. This should reduce the chance of developing OHSS.

## Missed Dose

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

## Administration

Dissolve the contents of one to six vials of Menopur® in 1 mL of sterile saline and ADMINISTER SUBCUTANEOUSLY immediately. Menopur® has been shown to retain its potency and be compatible with Bravelle® (urofollitropin for injection, purified) when they are mixed in the same syringe. 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.

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

# OVERDOSAGE

Aside from possible ovarian hyperstimulation (see **WARNINGS and PRECAUTIONS**), little is known concerning the consequences of acute overdosage with Menopur®.

# ACTION AND CLINICAL PHARMACOLOGY

## Mechanism of Action

Menopur®, administered for 7 to 20 days, produces 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 must be administered following Menopur® treatment, at a time when patient monitoring indicates sufficient follicular development has occurred.

## Pharmacodynamics

Menopur® is produced from urine of postmenopausal women. Human Chorionic Gonadotropin (hCG), a naturally occurring hormone in postmenopausal women, is present in Menopur® and contributes to the overall luteinizing hormone (LH) activity.

Menopur® 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 ovarian failure. FSH is the primary driver of follicular recruitment and growth in early folliculogenesis, while LH is important for ovarian steroidogenesis and is involved in the physiological events leading to development of a competent pre-ovulatory follicle. Follicular growth can be stimulated by FSH in the total absence of LH, but resulting follicles develop abnormally and are associated with low oestradiol levels and inability to luteinize to a normal ovulatory stimulus. In line with the action of LH activity in enhancing steroidogenesis, estradiol levels associated with treatment of Menopur® are higher than with recombinant FSH preparations. This should be considered when monitoring patient's response based on estradiol levels.

## Pharmacokinetics

### Absorption

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

### Distribution

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

### Metabolism

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

**Elimination**

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

Two open-label, randomized, controlled clinical studies were conducted to assess the pharmacokinetics of Menopur®. Study 2003-02 **(**compared single doses of SC administration of the US and European (EU) formulations of Menopur® 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 Menopur® 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 Tables 2 and 3.

**Table 2**
**FSH Pharmacokinetic Parameters (±SD) Following Menopur® Administration (Study 2003-02)**

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

**Table 3**
**FSH Pharmacokinetic Parameters Following Menopur® Administration (Study 2000-03)**

| PK Parameters | Single Dose (225 IU) | | Multiple Dose (225 IU x 1 day then 150 IU x 6 days) | |
|---|---|---|---|---|
| | SC | IM | SC | IM |
| $C_{max}$ (mIU/mL) | 8.5 | 7.8 | 15 | 12.5 |
| $T_{max}$ **(**hr) | 17.9 | 26.8 | 8.0 | 9 |
| AUC (hr-mIU/mL) | 726.2 | 656.1 | 622.7 | 546.2 |

Single dose AUC120 and multiple dose AUCss

## STORAGE AND STABILITY

Lyophilized powder may be stored refrigerated or at room temperature (15º to 25ºC). Protect from light. Use immediately after reconstitution. Discard unused material.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Menopur® (menotropins for injection, USP) is a purified preparation of gonadotropins extracted from the urine of post-menopausal women, which has undergone additional steps of purification. Each vial of Menopur® contains 75 International Units (IU) FSH activity and 75 IU LH activity, plus 21 mg Lactose Monohydrate and 0.005 mg Polysorbate 20 and Sodium Phosphate buffer (Sodium Phosphate Dibasic, Heptahydrate and Phosphoric Acid) in a sterile, lyophilized form intended for reconstitution with sterile 0.9% Sodium Chloride Injection, USP. Menopur® is administered by subcutaneous (SC) injection.

Menopur® (menotropins for injection, USP) is supplied in sterile vials as a lyophilized, white to off-white powder or pellet.

Each vial of Menopur® is accompanied by a vial of sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP: 75 IU FSH and 75 IU of LH activity, and supplied as: Box of 5 vials + 5 vials diluent.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

| | |
|---|---|
| **Drug Substance:** | Menotropins for injection |
| **Chemical Name:** | Human Menopausal Gonadotropin |
| **Structure:** | Menotropins contain Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). |
| **Physiochemical characteristics:** | Off-white to yellowish powder, soluble in water up to concentrations of approximately 200 mg/mL. Completely insoluble in ethanol, acetone and ether. |

## CLINICAL TRIALS

### Study Demographics and Trial Design

Table 4: Summary of patient demographics for clinical trials for in vitro fertilization.

| Table 4<br>Study Demographics and Trial Design | | | | | |
|---|---|---|---|---|---|
| **Study #** | **Trial Design** | **Dosage, Route of Administration and Duration** | **Number of Subjects** | **Mean Age Range** | **Gender** |
| IVF Study 0399E | Open-label, active-control, parallel-group, randomized, multi-centre. | Menopur® SC 75-450 IU QD<br>Gonal -F® 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>Repronex® 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><br>Phase I and II: Single dose Menopur® SC or IM 225 IU.<br>Phase I and II: Single dose Repronex® 225 IU SC and IM<br><br>Phase III: Single dose Menopur® SC or IM 225 IU.<br><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><br>Single dose; two 6-day testing periods each preceded by a 15-28 day pre-treatment period of Lupron® Depot 3.75 mg IM. | 57 | 18- 39 | Female |

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 (Gonal-F®) 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, Repronex®, administered SC , in infertile women undergoing an IVF cycle.

**Study Results**

In the IVF study 0399E, Menopur® was non-inferior to Gonal-F®-in terms of percentage of patients with an ongoing pregnancy in the treatment of women undergoing IVF/ICSI. This was true for both the ITT population and the PP population.

**Table 5**
**Primary Efficacy Parameter - Patients with Ongoing Pregnancy - Intent to Treat**
**IVF Study 0399E**

| Parameter | Menopur® n = 373 | | Gonal-F® n = 354 | | 95% CI[1] of difference | p-value[2] |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| Ongoing Pregnancy | 87 | 23.3 | 73 | 20.6 | -3.3, 8.7 | 0.42 |

[1] Not adjusted for centre
[2] Chi-Square test

**Table 6**
**Primary Efficacy Parameter - Patients with Ongoing Pregnancy - Per Protocol**
**IVF Study 0399E**

| Parameter | Menopur® n = 357 | | Gonal-F® n = 336 | | 95% CIg[1] of difference | p-value[2] |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| Ongoing Pregnancy | 85 | 23.8 | 71 | 21.1 | -3.5, 7.9 | 0.41 |

[1] Not adjusted for centre
[2] Chi-Square test

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 Repronex® SC in either the ITT or primary efficacy responder (received hCG) population as shown below.

| Table 7<br>Primary Efficacy Parameter: Number Oocytes Retrieved – Intent to Treat<br>IVF Study 2000-02 | | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Menopur® SC N = 61** | | **Repronex® 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 8<br>Primary Efficacy Parameter: Number Oocytes Retrieved Primary Efficacy Responders (Received hCG)<br>IVF Study 2000-02 | | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Menopur® SC N = 61** | | **Repronex® SC N = 62** | | **95 % CI** | **p-value[1]** |
| | **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 |

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 9 below.

| Table 9<br>Mean* (+ SD) Values and Comparisons for Baseline Corrected** Serum FSH Concentrations<br>Study 2003-02: | | | | |
|---|---|---|---|---|
| | EU Menopur® | US Menopur® | Test/Ref | 90% CI |
| $C_{max}$ (mIU/mL) | 11.43 ± 2.31 | 10.59± 3.07 | 92.72% | 83.19 -103.34% |
| $AUC_{0-120}$ (mIU•hr/mL) | 675.70 ± 162.53 | 651.65 ± 182.89 | 96.44% | 84.93 – 109.53% |
| $T_{max}$ (hr) | 18.85± 6.96 | 19.32± 6.27 | 102.48% | 86.52 – 118.44% |

* Reported values are least squared means

** Baseline correction is done by subtracting the mean of pre study baseline concentrations

## DETAILED PHARMACOLOGY

### Pharmacodynamics

### Assisted Reproductive Technologies (ART)

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.

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 Gonal-F® 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 lU/day for a total maximum duration of stimulation of 20 days. Treatment outcomes are summarized in Table 10.

| Table 10: Efficacy Outcomes for IVF Study 0399E (one cycle of treatment) | | |
|---|---|---|
| **Parameter** | **Menopur® SC n=373** | **Gonal F® 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) |

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 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. Treatment outcomes are summarized in Table 11.

| Table11: 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)

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 12.

**Table 12**
**Mean Number of Oocytes Retrieved**
**Intent To Treat**

| Controlled Study | Menopur® SC n=61 | Repronex® SC n=64 | p-value |
|---|---|---|---|
| IVF Study 2000-02 | 13.1 | 14.4 | 0.341 |
| | n=373 | Gonal-F® SC 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 Repronex® SC are shown in Tables 13, 14, and 15.

**Table 13**
**Patients with Chemical[1] Pregnancy**
**Intent To Treat**

| Controlled Study | n | Menopur® SC | | Repronex® SC | | p-value[2] |
|---|---|---|---|---|---|---|
| | | No. | % | No. | % | |
| IVF Study 2000-02 | 190 | 24 | 39.3 | 32 | 50 | 0.231 |
| | | | | Gonal-F® 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 14<br>Patients with Clinical[1] Pregnancy<br>Intent To Treat | | | | | | |
|---|---|---|---|---|---|---|
| Controlled Study | n | Menopur® SC | | Repronex® SC | | p-value[2] |
| | | No. | % | No. | % | |
| IVF Study 2000-02 | 190 | 18 | 29.5 | 26 | 40.6 | 0.193 |
| | | | | Gonal-F® 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 15<br>Patients with Continuing[1] Pregnancy<br>Intent To Treat | | | | | | |
|---|---|---|---|---|---|---|
| Controlled Study | n | Menopur® SC | | Repronex® SC | | p-value[2] |
| | | No. | % | No. | % | |
| IVF Study 2000-02 | 190 | 18 | 29.5 | 24 | 37.5 | 0.344 |
| | | | | Gonal-F® 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 16.

**Table 16**
**Mean Peak Serum $E_2$ Levels pg/mL**
**(Intent To Treat Population)**

| Controlled Study | n | Menopur® SC | | Repronex® SC | | p-value[1] |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | |
| FPI Purified Repronex® 2000-02 | 190 | 2007.1 | 1008.3 | 2462.8 | 1483.1 | 0.053 |
| | | | | Gonal-F® 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; 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 hCG criteria and total dose of gonadotropin administered in the IVF studies 0399E and 2000-02 between Menopur® SC and Repronex® SC are presented in Tables 17 and 18.

**Table 17**
**Number of Days to Meet hCG Criteria**

| Controlled Study | n | Menopur® SC | | Repronex® SC | | p-value[1] |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | |
| FPI Purified Repronex® 2000-02 | 190 | 9.60 | 1.40 | 9.4 | 1.40 | 0.356 |
| | | | | Gonal-F® SC | | |
| MFK/IVF/0399E | 727 | 11.54 | 1.91 | 11.52 | 2.00 | 0.860 |

[1] From one-way ANOVA

**Table 18**
**Average Total Dose of Gonadotropin**

| Controlled Study | n | Menopur® SC | | Repronex® SC | | p-value[1] |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | |
| FPI Purified Repronex® 2000-02 | 190 | 2625.0 | 847.7 | 2463.3 | 831.3 | 0.297 |
| | | | | Gonal-F® 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

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## PART III: CONSUMER INFORMATION

### Menopur®

This leaflet is Part III of a three-part "Product Monograph" published when Menopur® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Menopur®. Contact your doctor or pharmacist if you have any questions about the drug.

## ABOUT THIS MEDICATION

**What the medication is used for:**

Menotropins contain Follicle Stimulating Hormone and Luteinizing Hormone, two natural hormones produced in both males and females, and obtained from the urine of post menopausal women. These hormones help to maintain the normal function of the reproductive organs in both males and females.

Your doctor may have prescribed Menopur® because your pituitary gland does not release FSH (Follicle Stimulating Hormone), or it releases FSH and LH (Luteinizing Hormone) 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.

**What it does:**

Menopur® provides you with the FSH (Follicle Stimulating Hormone) 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, another hormone, hCG (human chorionic gonadotropin) is given mid cycle to mature the egg and induce ovulation.

**How long will one treatment cycle last?**

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.

**When it should not be used:**

Menopur® should **not** be used if:

1) You are pregnant.
2) You are breast-feeding.

Menopur® should also **not** be used if you have:

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

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

**What the medicinal ingredient is:**

Menopur® is a highly purified, sterile, freeze-dried powder for injection. It contains the active ingredient menotropins USP, 75 units FSH and 75 units LH.

**What the nonmedicinal ingredients are:**

Menopur® also contains lactose monohydrate, polysorbate 20, and sodium phosphate and

phosphoric buffer (sodium phosphate dibasic, heptahydrate and phosphoric acid).

**What dosage forms it comes in:**

Menopur® is a sterile, lyophilized form intended for reconstitution with sterile 0.9% sodium chloride solution for injection. Menopur® is administered by subcutaneous (SC) [tissue under your skin] injection.

## WARNINGS AND PRECAUTIONS

**Will Menopur® put me at risk for reproductive complications?**

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.

## INTERACTIONS WITH THIS MEDICATION

There have been no drug interactions reported with this medication.

## PROPER USE OF THIS MEDICATION

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, do not panic, but you should call your doctor for advice.

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.

**Instructions for Reconstitution and Subcutaneous Administration.**

Your doctor has prescribed Menopur® for subcutaneous injection. This means that is it 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 Sodium Chloride 0.9% (sterile diluent) that 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 the Sodium Chloride (sterile diluent) provided 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 STERILE SALINE FOR 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**

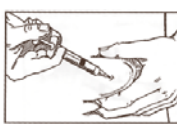
  B. Turn vial upside down, pull back on plunger to withdraw solution as you slowly lower needle.

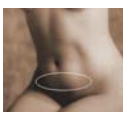
**3. Changing the Needle**


- 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. Dispose 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 provider how to properly dispose of the needle disposal container.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Symptom / effect | | Talk with your doctor or pharmacist | | Call your doctor or pharmacist |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| Common | Mild OHSS | | ✓ | ✓ |
| Uncommon | Severe OHSS | | ✓ | ✓ |

*This is not a complete list of side effects. If you have any unexpected effects after receiving Menopur®, contact your doctor or pharmacist.*

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

***NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found by contacting the sponsor, **Ferring Inc.**, at: **1-866-373-1333.**

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