PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**MENOPUR®**

Menotropins for Injection

Powder for Solution, 75 IU / Vial (75 IU FSH / 75 IU LH), For SC Use Only

Gonadotropins for Infertility

Ferring Inc.

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Toronto, Ontario

M2J 5C1

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH 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 an 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

MENOPUR is not used in pediatric populations.

1.2 Geriatrics

MENOPUR is not used in geriatric populations.

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 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. 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, 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 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.

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.

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

MENOPUR Vial #	Vial size	Volume of diluent to be added to MENOPUR 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

MENOPUR Vial #	Vial size	Volume of diluent to be added to MENOPUR vial	Approximate available volume	Concentration per mL
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 OVERDOSAGE

Aside from possible ovarian hyperstimulation (see **7 WARNINGS AND PRECAUTIONS**), little is known concerning the consequences of acute overdosage with MENOPUR.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

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 and 75 IU LH)	Lactose Monohydrate, Polysorbate 20 Sodium Phosphate Buffer (sodium phosphate dibasic heptahydrate, and phosphoric acid)
FSH = Follicle stimulating hormone LH = Luteinizing hormone		

MENOPUR (menotropins for injection) 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 in a sterile, lyophilized form intended for reconstitution with sterile 0.9% Sodium Chloride Injection, USP. Human Chorionic Gonadotropin (hCG), a naturally occurring hormone in postmenopausal urine, is present in MENOPUR and contributes to the overall luteinizing hormone activity. MENOPUR is administered by subcutaneous (SC) injection.

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 7 **WARNINGS AND PRECAUTIONS, 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 Mutagenesis

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 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.

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, 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.

Multiple Pregnancies

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.

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 **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 **Monitoring and Laboratory Tests** above), 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.

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).

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.

Renal

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

7.1 Special Populations

7.1.1 Pregnant Women

See **2 CONTRAINDICATIONS** section.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

MENOPUR is not used in pediatric populations.

7.1.4 Geriatrics

MENOPUR is not used in geriatric populations.

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 **7 WARNINGS AND PRECAUTIONS – *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. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 $\geq$1 % in women treated with MENOPUR are listed in Table 1.

Table 1: MENOPUR subcutaneous (SC) and intramuscular (IM) in female patients undergoing IVF and OI adverse events with onset on and after GnRH administration, COSTART Classification (or 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
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

	IVF * N = 499		OI ** N = 76	
Body systems/preferred term	**N**	**%**	**N**	**%**
Strep Throat	0	0.0	1	1.3
Skin/Appendages				
Pruritus	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

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 erythemia, and vaginal and genital swelling

8.5 Post-Market Adverse 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.

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

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

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

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.

10.2 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.

10.3 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 Table 2 and Table 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

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.

12 SPECIAL HANDLING INSTRUCTIONS

None. MENOPUR does not require special handling.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Menotropins for injection
Chemical name:	Human Menopausal Gonadotropin
Structure:	Menotropins contain Follicle Stimulating Hormone (FSH) 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.

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

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 4 - Summary of patient demographics for clinical trials for *in vitro* fertilization

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
IVF Study 0399E	Open-label, active-control, parallel-group, randomized, multi-centre.	MENOPUR SC 75-450 IU QD 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 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) Three Phases: (I, II, and III) spaced 7 days apart. Phase I and II: Single dose MENOPUR SC or IM 225 IU. Phase I and II: Single dose REPRONEX 225 IU SC and IM	33	18-39	Female

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
		Phase III: Single dose MENOPUR SC or IM 225 IU. 225 IU on day 1 followed by 150 IU QD x 6 days			
BE Study 2003-02	Multi-centre, open-label, randomized, single-dose, two period cross-over study.	US MENOPUR SC 400 IU EU MENOPUR SC 400 IU 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
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 (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.

14.2 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 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 IU/day for a total maximum duration of stimulation of 20 days. Treatment outcomes are summarized in Table 5.

Table 5: 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)

E_2 = estradiol

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 Intent-To-Treat (ITT) population and the Per Protocol (PP) population.

Table 6 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 7 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

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 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 8.

Table 8: 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 REPRONEX SC in either the ITT or primary efficacy responder (received hCG) population as shown below.

Table 9
Primary Efficacy Parameter: Number Oocytes Retrieved – Intent to Treat
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 10 Primary Efficacy Parameter: Number Oocytes Retrieved Primary Efficacy Responders (Received hCG) 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

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 11.

Table 11 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 Table 12, Table 13, and Table 14.

Table 12 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 13 Patients with Clinical[1] Pregnancy 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 14 Patients with Continuing[1] Pregnancy 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 15.

Table 15 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 Table 16 and Table 17.

Table 16 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 17 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

14.3 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 18 below.

Table 18 Mean* (+ SD) Values and Comparisons for Baseline Corrected** Serum FSH Concentrations 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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether [Brand name] affects fertility in males or females.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MENOPUR

Menotropins for Injection

Read this carefully before you start taking **MENOPUR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MENOPUR**.

What is MENOPUR 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.

How does MENOPUR work?

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.

What are the ingredients in MENOPUR?

Medicinal ingredients: Menotropins – 75 units FSH and 75 units LH.

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 forms:

Sterile lyophilized powder, 75 IU / vial

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.
- 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 of a specialist having the required facilities for laboratory monitoring.

Other warnings you should know about:

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.

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

The following may interact with MENOPUR:

- There have been no drug interactions reported with this medication.

How to take MENOPUR:

MENOPUR must be taken by injection.

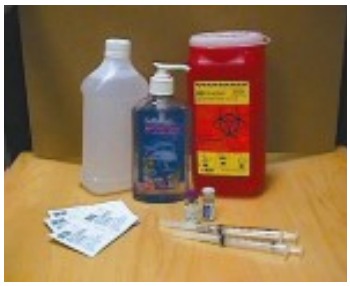
Every treatment is individualized. Yours has been carefully designed for you by your doctor according to your own specific needs. It is very important that you keep your appointments and follow your doctor's instructions, particularly with regard to the amount and frequency of the medication you are 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, do not panic, but you should 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**

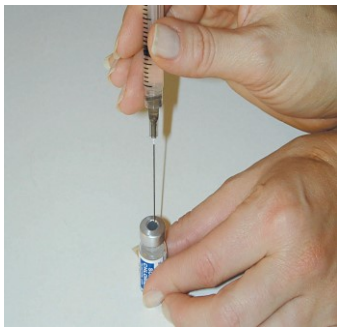


- Wash your hands with antibacterial soap and use alcohol to clean the area you will be working on.
- Have these supplies ready:
  - Vial (or vials) of MENOPUR, 75 IU
  - A vial of 0.9% Sodium Chloride (sterile diluent). If you have the kit, the diluent is conveniently packaged with MENOPUR
  - A syringe 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.

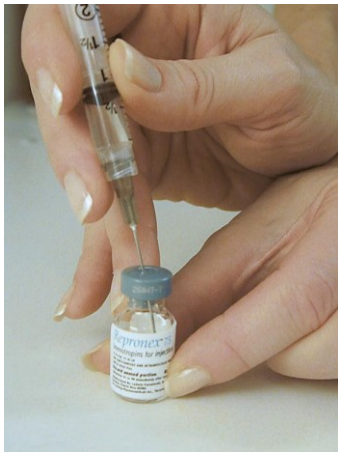


- Wipe tops of vials with alcohol to sterilize them. Don't touch tops of vials once you have sterilized them.
- Uncap needle by carefully twisting needle cap clockwise and pulling cap upward. Avoid twisting needle counterclockwise, as this can cause needle to separate from syringe.
- Insert needle through 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.

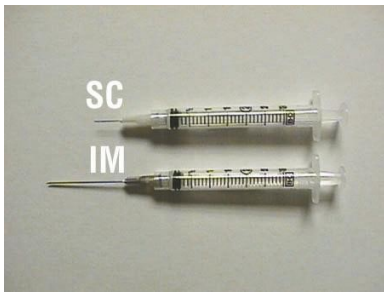
This can be accomplished by reconstituting a single vial as described above (see step 2). Then draw the entire contents of the first vial into a syringe, and inject the contents into a second vial of lyophilized MENOPUR. Gently swirl the second vial as described above, once again checking to make sure 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.

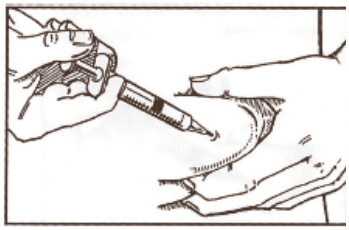
3) Changing the Needle

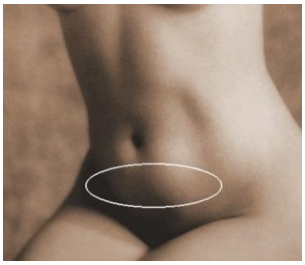


- While holding syringe upward, replace needle cap and remove large needle by twisting it counterclockwise. Replace with the small, subcutaneous needle by twisting it clockwise onto syringe.
- Hold syringe straight up. Draw back slightly on plunger and tap syringe so that *any* air bubbles rise to top. 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 provider 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, or regional poison control centre immediately, even if there are no symptoms.

What are 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			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or

Calling toll-free at 1-866-234-2345.

NOTE: Contact your health 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 this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; Ferring Inc.'s website: www.ferring.ca, or by calling 1-866-384-1314.

This leaflet was prepared by Ferring Inc.

Last Revised June 1, 2021