PRODUCT MONOGRAPH

[Pr]Repronex®

(Menotropins for Injection)

75 IU/Vial

(75 IU FSH, 75 IU LH)

For SC/IM Use Only

Gonadotropins for Infertility

Ferring Inc.
200 Yorkland Boulevard
Suite 500
North York, Ontario
M2J 5C1

Control #: 197382 **Date of Approval:** November 17, 2016

DESCRIPTION

Repronex (menotropins for injection) is a purified preparation of gonadotropins extracted from the urine of postmenopausal women. Human Chorionic Gonadotropin (hCG) a naturally occurring hormone in postmenopausal urine, is detected in Repronex. Each vial of Repronex contains 75 International Units (IU) of follicle-stimulating hormone (FSH) activity and 75 IU of luteinizing hormone (LH) activity, respectively, plus 20 mg lactose monohydrate in a sterile, lyophilized form. The final product may contain sodium phosphate buffer (sodium phosphate tribasic and phosphoric acid). Both FSH and LH are acidic and water soluble. Repronex is administered by subcutaneous or intramuscular injection.

ACTIONS AND CLINICAL PHARMACOLOGY

Repronex (menotropins for injection) administered for seven to twelve days produces ovarian follicular growth in women who do not have primary ovarian failure. Treatment with menotropins in most instances results only in follicular growth and maturation. In order to effect ovulation, human chorionic gonadotropin (hCG) must be given following the administration of menotropins when clinical assessment of the patient indicates that sufficient follicular maturation has occurred. [1,7]

In an early pharmacokinetic study including 16 healthy female volunteers, 300 IU menotropins were administered subcutaneously (SC) and intramuscularly (IM) in a crossover study, after patients endogenous FSH and LH were suppressed. Measurements of serum FSH concentrations indicated that SC administration leads to higher values for both C_{max} and $AUC_{(0-\%)}$ when compared to IM injections.

The subcutaneous and intramuscular routes were not bioequivalent. Compared to IM administration, the SC administration of menotropins results in an increase of FSH C_{max} and $AUC_{(0-4)}$ by 35 and 20% respectively.

Clinical studies for ovulation induction (in women with anovulatory or oligoovulatory infertility) and in-vitro fertilization showed enhanced follicular development, induction of ovulation, and clinical pregnancies.

INDICATIONS AND CLINICAL USE

Repronex (menotropins for injection) and hCG given in a sequential manner are indicated for multiple follicular development (controlled ovarian stimulation) and induction of ovulation in infertile patients who have previously received pituitary suppression.

CONTRAINDICATIONS

Repronex (menotropins for injection) is contraindicated in women who have:

- A high FSH level indicating primary ovarian failure.
- Uncontrolled thyroid and adrenal dysfunction.
- An organic intra cranial lesion such as a pituitary tumor.
- The presence of any cause of infertility other than anovulation unless they are candidates for *in vitro*-fertilization.
- Abnormal bleeding of undetermined origin.
- Ovarian cysts or enlargement not due to polycystic ovary syndrome.
- Prior hypersensitivity to menotropins.

Repronex is contraindicated in women who are pregnant. There are limited human data on the effects of menotropins when administered during pregnancy.

WARNINGS

Repronex (menotropins for injection) 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 PRECAUTIONS - Laboratory Tests).

Overstimulation of the Ovary During Repronex 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 those treated with Repronex and hCG, and generally regresses without treatment within two or three weeks.

In order to minimize the hazard associated with the occasional abnormal ovarian enlargement which may occur with Repronex and hCG therapy, the lowest dose consistent with expectation of good results, should be used. Careful monitoring of ovarian response can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of Repronex therapy, hCG should not be administered in this course of therapy; this will reduce the chances of development of the ovarian Hyperstimulation Syndrome.

The 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 below). 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 Ovarian Hyperstimulation Syndrome (OHSS).

OHSS occurs in approximately 0.4% of patients when the recommended dose is administered and in 1.3% of patients when higher than recommended doses are administered. OHSS occurred in 3 of 125 (2.4%) Repronex treated women during the In Vitro Fertilization (IVF) clinical study. None of these cases was classified as severe. In the Ovulation Induction (OI) clinical study, 4 of 72 (5.5%) Repronex treated women developed OHSS and of this number one case was classified as severe (1.4%). 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 PRECAUTIONS - Laboratory Tests), the hCG should be withheld.

If OHSS occurs, treatment should be stopped and the patient hospitalized. Treatment is primarily symptomatic, consisting of bed rest, fluid and electrolyte management, and analgesics if needed. The phenomenon of hemoconcentration associated with fluid loss into the peritoneal cavity, pleural cavity, and the pericardial cavity has been seen to occur and should be thoroughly assessed in the following manner: 1) fluid intake and output, 2) weight, 3) hematocrit, 4) serum and urinary electrolytes, 5) urine specific gravity, 6) BUN and creatinine, and 7) abdominal girth. These determinations are to be performed daily or more often if the need arises.

With OHSS there is an increased risk of injury to the ovary. The ascitic, pleural, and pericardial fluid should not be removed unless absolutely necessary to relieve symptoms such as pulmonary distress or cardiac tamponade. Pelvic examination may cause rupture of an ovarian cyst, which may result in hemoperitoneum, and should therefore be avoided. If this does occur, and if bleeding becomes such that surgery is required, the surgical treatment should be designed to control bleeding and to retain as much ovarian tissue as possible. Intercourse should be prohibited in those patients in whom significant ovarian enlargement occurs after ovulation because of the danger of hemoperitoneum resulting from ruptured ovarian cysts.

The management of OHSS may be divided into three phases: the acute, the chronic, and the resolution phases. Because the use of diuretics can accentuate the diminished

intravascular volume, diuretics should be avoided except in the late phase of resolution as described below.

Acute Phase:

Management during the acute phase should be designed to prevent hemoconcentration due to loss of intravascular volume to the third space and to minimize the risk of thromboembolic phenomena and kidney damage. Treatment is designed to normalize electrolytes while maintaining an acceptable but somewhat reduced intravascular volume. Full correction of the intravascular volume deficit may lead to an unacceptable increase in the amount of third space fluid accumulation. Management includes administration of limited intravenous fluids, electrolytes, and human serum albumin. Monitoring for the development of hyperkalemia is recommended.

Chronic Phase:

After stabilizing the patient during the acute phase, excessive fluid accumulation in the third space should be limited by instituting severe potassium, sodium, and fluid restriction.

Resolution Phase:

A fall in hematocrit and an increasing urinary output without an increased intake are observed due to the return of third space fluid to the intravascular compartment. Peripheral and/or pulmonary edema may result if the kidneys are unable to excrete third space fluid as rapidly as it is mobilized. Diuretics may be indicated during the resolution phase if necessary to combat pulmonary edema.

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 Ovarian Hyperstimulation Syndrome 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 Births

Multiple pregnancies have occurred following treatment with Repronex IM and SC. In a clinical trial for ovulation induction in which Repronex IM and Repronex SC were directly compared, the rates of multiple pregnancies were as follows. Of the four clinical pregnancies with Repronex IM, two were single and two were multiple pregnancies. Both multiple pregnancies were triplet pregnancies. Of the six clinical pregnancies with Repronex SC**,** three were single and three were multiple pregnancies. The three multiple

pregnancies included one twin pregnancy and two quadruplet pregnancies.

In a clinical trial of IVF patients in which Repronex IM and Repronex SC were directly compared, the rates of multiple pregnancies were as follows: Of the twenty four continuing pregnancies on Repronex IM, fourteen were single and ten were multiple pregnancies. The ten multiple pregnancies included three triplet and seven twin pregnancies. Of the twenty nine continuing pregnancies on Repronex SC, fourteen were single and fifteen were multiple pregnancies. The fifteen multiple pregnancies included three quadruplet, three triplet and nine twin pregnancies. The patient and her partner should be advised of the frequency and potential hazards of multiple gestation before starting treatment.

Hypersensitivity/Anaphylactic Reactions

Hypersensitivity/anaphylactic reactions associated with menotropins administration have been reported in some patients. These reactions presented as generalized urticaria, facial edema, angioneurotic edema, and/or dyspnea suggestive of laryngeal edema. The relationship of these symptoms to uncharacterized urinary proteins is uncertain.

PRECAUTIONS

General

Careful attention should be given to diagnosis in the selection of candidates for menotropins therapy (see INDICATIONS; PRECAUTIONS).

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 THE CONSUMER

Prior to therapy with Repronex (menotropins for injection), 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 section) and the risk of multiple births should be discussed.

Selection of Patients

Before treatment with Repronex is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. Except for those patients enrolled in an *in vitro* fertilization program, this should include a hysterosalpingogram (to rule out uterine and tubal pathology) and documentation of anovulation by means of basal body temperature, serial vaginal smears, examination of cervical mucus, determination of serum (or urine) progesterone, urinary pregnanediol and endometrial biopsy. Patients with tubal pathology should receive menotropins only if enrolled in an *in vitro* fertilization 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 anovulatory disorders. Cervical dilation and curettage should always be done for diagnosis before starting Repronex therapy in such patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities. Evaluation of the partner's fertility potential should be included in the workup.

Pregnancy

See CONTRAINDICATIONS

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 is administered to a nursing woman.

Drug Interactions

No clinically significant drug/drug or drug/food adverse interactions have been reported during menotropins therapy.

Laboratory Tests

Treatment for induction of ovulation

In most instances, treatment with menotropins results only in follicular growth and maturation. In order to effect ovulation, hCG must be given following the administration of Repronex when clinical assessment of the patient indicates that sufficient follicular maturation has occurred. This may be directly estimated by measuring serum (or urinary) estrogen levels and sonographic visualization of the ovaries. The combination of both estradiol levels and ultrasonography are useful for monitoring the growth and development of follicles, timing hCG administration, as well as minimizing the risk of the Ovarian Hyperstimulation Syndrome and multiple gestation. Other clinical parameters which may have potential use for monitoring menotropins therapy include:

- Changes in the vaginal cytology;
- Appearance and volume of the cervical mucus;
- Spinnbarkeit; and
- Ferning of the cervical mucus.

The above clinical indices provide an indirect estimate of the estrogenic effect upon the target organs, and therefore should only be used adjunctively with more direct estimates of follicular development, i.e., serum estradiol and ultrasonography.

The clinical confirmation of ovulation, with the exception of pregnancy, is obtained by direct and indirect indices of progesterone production. The indices most generally used are as follows:

- A rise in basal body temperature;
- Increase in serum progesterone; and

- 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:

- Fluid in the cul-de-sac;
- Ovarian stigmata; and
- Collapsed follicle.

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

Carcinogenesis/Mutagenesis

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

ADVERSE REACTIONS

The following adverse reactions, reported during menotropins therapy, are listed in decreasing order of potential severity: pulmonary and vascular complications (see WARNINGS); ovarian hyperstimulation syndrome (see WARNINGS); hemoperitoneum; adnexal torsion (as a complication of ovarian enlargement); mild to moderate ovarian enlargement; ovarian cysts; abdominal pain; sensitivity to menotropins (febrile reactions suggestive of allergic response have been reported following the administration of menotropins. Reports of flu-like symptoms including fever, chills, musculoskeletal aches,

joint pains, nausea, headaches, and malaise have also been reported); gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal cramps, bloating); pain, rash, swelling and/or irritation at the site of injection; body rashes; dizziness, tachycardia, dyspnea, and tachypnea.[1]

The following medical events have been reported subsequent to pregnancies resulting from menotropins therapy: etopic pregnancy; congenital abnormalities.[1]

From a study of 287 completed pregnancies following menotropins-hCG therapy, five incidents of birth defects were reported (1.7%). One infant had multiple congenital anomalies consisting of imperforate anus, aplasia of the sigmoid colon, third degree hypospadias, cecovesicle fistula, bifid scrotum, meningocele, bilateral internal tibial torsion, and right metatarsus adductus. Another infant was born with an imperforate anus and possible congenital heart lesions; another had a supernumerary digit; another was born with hypospadias and exstrophy of the bladder; and the fifth child had Down's syndrome. None of the investigators felt that these defects were drug-related. Subsequently one report of an infant death due to hydrocephalus and cardiac anomalies has been received. [1]

There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for ovulation induction; however, a causal relationship has not been established.[1]

In the two randomized, controlled clinical studies, comparing Repronex (menotropins for injection) IM, Repronex SC and Pergonal IM in patients undergoing IVF and in patients

with polycystic ovary disease and other diagnoses causing anovulation for ovulation induction, the adverse events occurring in $<$ 1% of patients exposed to Repronex IM or Repronex SC are described in Table 1 below.

Table 1: Patients with Adverse Events < 1%

	Repronex IM N=101	**Repronex SC N =96**
Adverse Event	n (%)	n (%)
Injection Site AEs		
Injection Site Edema	1 (1.0)	8 (8.3)*
Injection Site Reaction	2 (2.0)	8 (8.3)*
Genitourinary/Reproductive AEs		
OHSS	2 (2.0)	5 (5.2)
Vaginal Hemorrhage	8 (7.9)	3 (3.1)
Ovarian Disease	3 (3.0)	8 (8.3)
Ectopic Pregnancy	1 (1.0)	1 (1.0)
Pelvic Pain	3 (3.0)	1 (1.0)
Breast Tenderness	2 (2.0)	2 (2.1)
Gastrointestinal AEs		
Nausea	4 (4.0)	7 (7.3)
Vomiting	0 (0.0)	3 (3.1)
Diarrhea	0 (0.0)	2 (2.1)
Abdominal Cramping	7 (6.9)	5 (5.2)
Abdominal Pain	5 (5.0)	7 (7.3)
Enlarged Abdomen	6 (6.0)	2 (2.1)
Other Body System AEs		
Headache	6 (6.0)	5 (5.2)
Infection	1 (1.0)	0(0.0)
Dyspnea	1 (1.0)	2 (2.1)

* Fisher=s Exact/Chi-Squared Tests - significant for Repronex SC vs. Repronex IM.

Post-Market Experience

Repronex has been marketed in the United States since 1997. All adverse events reported have been non-serious and expected reactions, and were predominantly injection site reactions, as well as fever, malaise and nausea. These reactions abated and resolved without sequelae.

SYMPTOMS AND TREATMENT OF OVER DOSAGE

Aside from ovarian hyperstimulation (see WARNINGS), little is known concerning the consequences of acute overdosage with menotropins.

DOSAGE AND ADMINISTRATION

Dosage:

Infertile Patients with Oligo-Anovulation:

The dose of Repronex (menotropins for injection) to produce maturation of the follicle must be individualized for each patient. It is recommended that the initial dose of Repronex to any patient should be 150 IU (for any patient receiving leuprolide or other GnRH therapy) of FSH/LH per day, for five days. Based on clinical monitoring (ultrasound results and serum estradiol concentrations) 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 more than 75 to 150 IU per adjustment. The maximum daily dose of Repronex should not exceed 450 IU and dosing beyond 12 days is not recommended.

If patient response to Repronex is appropriate, hCG (5000 to 10,000 units) should be given one day following the last dose of Repronex. The hCG should be withheld if the

serum estradiol is greater than 2000 pg/mL, if the ovaries are abnormally enlarged or if abdominal pain occurs, and the patient should be advised to refrain from intercourse. These precautions may reduce the risk of development of the Ovarian Hyperstimulation Syndrome and multiple gestation.

During treatment with both Repronex and hCG and during a two-week post-treatment period, and patients should be examined at least every other day for signs of excessive ovarian stimulation. Most of the Ovarian Hyperstimulation Syndrome occurs after treatment has been discontinued and reaches its maximum at about seven to ten days post-ovulation. If there is inadequate follicle development or follicle development or ovulation without subsequent pregnancy, the course of treatment with gonadotropins may be repeated.

The couple should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG until ovulation becomes apparent from the indices employed for the determination of progestational activity. Care should be taken to insure insemination. In the light of the foregoing indices and parameters mentioned, it should become obvious that, unless a physician is willing to devote considerable time to these patients and be familiar with and conduct the necessary laboratory studies, he/she should not use Repronex.

Assisted Reproductive Technologies

The recommended initial dose of Repronex for patients who have received GnRH agonist or antagonist 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 more than 75 to 150 IU per adjustment. The maximum daily dose of Repronex given should not exceed 450 IU and dosing beyond 12 days is not recommended.

Once adequate follicular development is evident, hCG (5000 - 10,000 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.

Administration

Dissolve the contents of one to six vials of Repronex in one to two mL of 0.9% Sodium Chloride Injection and **ADMINISTER SUBCUTANEOUSLY OR INTRAMUSCULARLY** immediately. Any unused reconstituted material should be discarded.

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

PHARMACEUTICAL INFORMATION

Composition

Each vial of Repronex contains 75 International Units (IU) of follicle-stimulating hormone (FSH) activity and 75 IU leutinizing hormone (LH) activity, plus 20 mg lactose monohydrate in a sterile, lyophilized form. By biological assay, one IU of LH for the Second International Reference Preparation for hMG is biologically equivalent to approximately 0.5 U of hCG.

Stability and Storage Recommendations

Lyophilized powder may be stored at 15°C - 25ºC. Protect from light.

Reconstituted Solutions

Use immediately after reconstitution. Discard unused material.

AVAILABILITY OF DOSAGE FORMS

Repronex (menotropins for injection) is supplied in vials of 75 IU (75 IU FSH and 75 IU LH activity) as a sterile, lyophilized, white to off-white powder, with a 2 mL vial of diluent (0.9% Sodium Chloride Injection, USP).

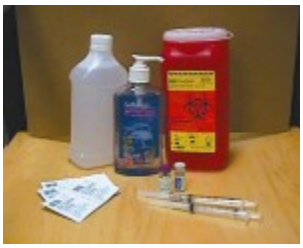
Boxes 5 vials + 5 vials diluent

INFORMATION FOR THE CONSUMER

Instructions for Reconstitution and Subcutaneous Administration

Your doctor has just prescribed Repronex 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 Repronex, 75 IU
- A vial of Sodium Chloride 0.9% (sterile diluent) that is conveniently packaged with Repronex
- A syringe and sterile needles (check with your doctor about which syringe and needle size to use)

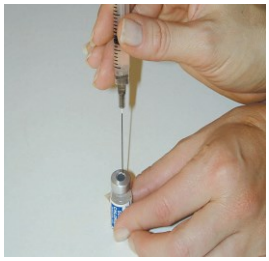
- Alcohol pads and rubbing alcohol
- Gauze and cotton balls
- A needle disposal container

2. Preparing your medicine and filling the syringe

Remember: *Only the Sodium Chloride (sterile diluent) provided must be used to reconstitute Repronex.*

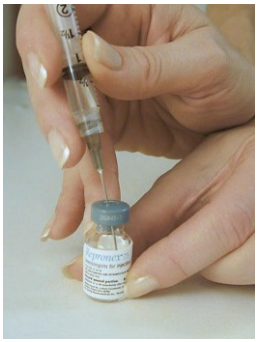
- Remove syringe and larger needle from the wrapper. While holding the protective cap, twist needle clockwise to make sure needle is secure. Set it aside.
- Remove plastic caps from tops of vials of Repronex and sterile diluent.
- Wipe tops of vials with alcohol to sterilize them. Don′t touch tops of 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 vial.



- 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 Repronex powder, aiming sterile diluent at side of vial to avoid creating bubbles. The solution should be clear and colorless.

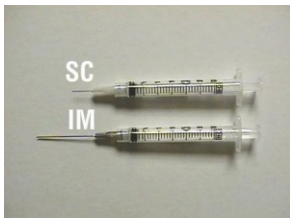
  The Repronex powder will dissolve quickly do not shake vial because this will create bubbles.
- As soon as powder has completely dissolved, withdraw all Repronex solution into syringe. There are two ways of doing this:



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.

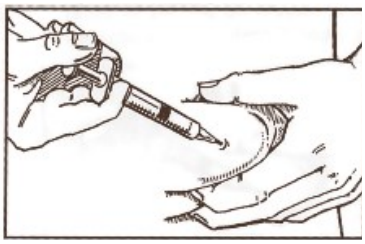
3. Changing the needle

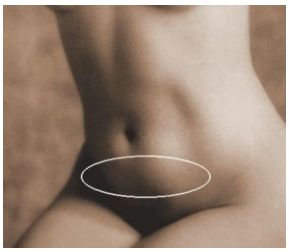


- While holding syringe upward, replace needle cap and remove large needle by twisting it counterclockwise. Replace with the small, subcutaneous needle by twisting it clockwise onto syringe.
- Hold syringe straight up. Draw back slightly on plunger and tap syringe so that *any* air bubbles rise to top. 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.
- Repronex solution is now ready for injection.

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

4. **Injecting Your Medicine**





Repronex should be injected into a skin fold on your abdomen a few inches below your navel...left or right. Each day, use the alternative 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 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.

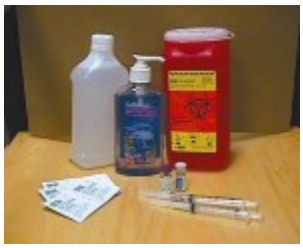
5. Dispose of the Syringe and Needles

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.

Instructions for Reconstitution and Intramuscular Administration

Your doctor has just prescribed Repronex for intramuscular injection. Intramuscular injection requires another person (partner) to administer the injection. This instruction sheet, will help you and your partner 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.

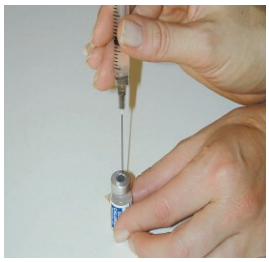
- Have these supplies ready:
- Vial (or vials) of Repronex, 75 IU
- A vial of Sodium Chloride 0.9% (sterile diluent) that is conveniently packaged with Repronex
- A syringe and sterile needles (check with your doctor about which syringe and needle size to use)
- Alcohol pads and rubbing alcohol
- Gauze and cotton balls

- A needle disposal container

2. **Preparing Your Medicine and Filling the Syringe**

Remember: *Only the Sodium Chloride (sterile diluent) provided must be used to reconstitute Repronex*

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

- Do not tap the point of needle against sides or bottom of vial because it may dull or bend the tip.
- 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 Repronex powder, aiming sterile diluent at side of vial to avoid creating bubbles. The solution should be clear and colorless.

The Repronex powder will dissolve quickly do not shake vial because this will create bubbles.

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

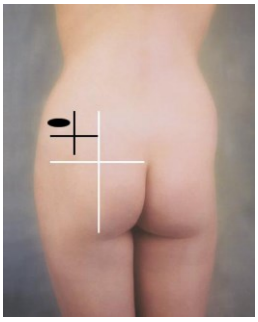
    A. Leave vial on counter, tilt it, pull back on plunger to withdraw all solution, **OR**

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

- 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.
- Repronex solution is now ready for injection.

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

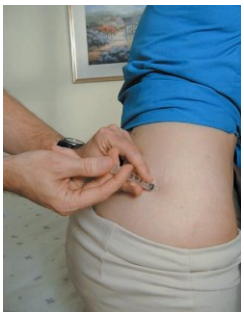
3. Instructions for the Person (Partner) Administering the Injection



- Repronex should be injected into muscle of either the right or left upper buttock, below the hipbone. Below, we will describe a left-side injection.
- To locate injection site, stand directly behind person who is to receive injection. Imagine that the left buttock is divided into quadrants. The injection should be given in the upper left-hand corner of the upper left-hand quadrant (see diagram).
- Swab area with alcohol, and allow to air-dry.

Ask the person receiving the injection to stand pigeon-toed or bend her leg slightly (same leg as the injection site), placing her weight on the other foot. This will relax the muscle being injected and greatly reduce muscle soreness.

4. Injecting Your Medicine



- Uncap needle and insert it straight into skin in one smooth motion until needle disappears.
- To make sure you haven=t hit a blood vessel, pull back a little on the plunger. If you don=t see blood in the syringe, you can proceed with injection.
- If you ever do hit a blood vessel, and see blood in the syringe, always withdraw the needle and replace needle with a new one. Then repeat injection process.
- Slowly push plunger all the way in, until you have injected all the Repronex.
- Pull syringe straight out again, using one smooth motion.
- If you have a little bleeding after the injection, don=t worry. Just press the site with cotton for about 10 seconds, and cover it with an adhesive bandage

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.

PHARMACOLOGY

Pharmacokinetics

In an early pharmacokinetic study performed during product development, single dose pharmacokinetics for FSH were determined following intramuscular and subcutaneous administration of 300 IU LH and 300 IU FSH to 16 healthy down-regulated female volunteers.

The subcutaneous and intramuscular routes were not bioequivalent. Compared to IM administration, the SC administration of menotropins results in an increase of FSH C_{max} and $AUC_{(0-4)}$ by 35 and 20% respectively.

Table 2a: Pharmacokinetic Parameters (Mean ± SD) of FSH following Administration of Menotropins *		
	Healthy Female Volunteers	
	Single Dose (300) FSH	
	Intramuscular	**Subcutaneous**
AUC $_{(0-4)}$ (mIUAh/mL)**	320.1	385.2
C max (mIU/mL)**	4.15	5.62
t max (h)***	18	12
Cl/F (L/hr)	0.94 ± 0.07	0.77 ± 0.13
V/F (L)	57.7 ± 6.57	39.4 ± 5.5
Ka (hr $^{-1}$)	0.12 ± 0.02	0.13 ± 0.05

Cl - Clearance, V - volume of distribution, Ka - absorption rate

* - Menotropins product used during Ferring drug development.

** - Geometric mean.

*** -Geometric median.

Single dose and steady state pharmacokinetics for FSH and LH of Repronex were determined following daily intramuscular and subcutaneous administration in two groups (totalling 35 patients) of pituitary down-regulated women undergoing ovulation induction. These data are presented in Table 2b below.

The data presented in the table below (Table 2b) are pharmacokinetic parameters derived from the pharmacokinetic portion of the ovulation induction trial, were the pharmacokinetic profile of single and multiple doses of Repronex IM and SC were investigated for these patients. The elimination half-life was calculated by classic pharmacokinetic approach while the total body clearance, volume of distribution/clearance, and absorption rate was calculated by population pharmacokinetic approach.

Table 2b: Pharmacokinetic Parameters (Mean ± SD) of FSH and LH Following Administration of Repronex				
	OI Patients			
	Multiple Dose IM (150)		**Multiple Dose SC (150)**	
	FSH	**LH**	**FSH**	**LH**
t_2 terminal (hr)	12.7	17.1	31.6	6.95
* Cl/F (L/hr)	1.10 ± 0.23	3.15 ± 0.41	0.97 ± 1.37	5.07 ± 3.48
* V/F (L)	20.2 ± 9.71	77.91 ± 23.94	44.4 ± 21.41	41.17 ± 28.29
* Ka (hr^{-1})	0.22 ± 0.23	0.04 ± 0.02	0.42 ± 0.42	0.23 ± 0.67

Cl - Clearance, V - volume of distribution, Ka - absorption rate

* Calculated by baseline background subtraction.

For FSH the subcutaneous route of administration had a slightly faster absorption rate than the intramuscular route in both volunteers and patients.

Absorption

The geometric mean of FSH C_{max} and AUC_{0-4} upon single dose SC administration of menotropins is 5.62 mIU/mL and 385.2 mIU-h/mL, respectively; the corresponding geometric median of FSH t_{max} is 12 hours. The geometric mean of FSH C_{max} and AUC_{0-4} upon single dose IM administration of menotropins is 4.15 mIU/mL and 320.1 mIU-h/mL, respectively; the corresponding geometric median of FSH t_{max} is 18 hours.

Distribution

Human tissue or organ distribution of FSH and LH have not been determined for Repronex.

Metabolism

FSH and LH metabolism following administration of Repronex has not been studied in humans.

Clearance of FSH in volunteers was 0.77 L/hr SC and 0.94 L/hr IM. Clearance of FSH in patients was 0.97 L/hr SC and 1.10 L/hr IM. Clearance of LH in patients was 5.07 L/hr SC and 3.15 L/hr IM.

Following IM administration of a single dose of menotropins, approximately 8% of the dose appears to be excreted unchanged in the urine.

Excretion

The mean elimination half-lives of FSH upon single dose SC and IM administration of menotropins are 53.7 and 59.2 hours, respectively.

Pharmacodynamics

The results of the clinical experience and effectiveness of the administration of menotropins to 1,286 patients in 3,002 courses of therapy are summarized below. The values include patients who were treated with other than the recommended dosage regime. The values for the presently recommended dosage regime are essentially the same. [1]

	%
Patients ovulating	75
Patients pregnant	25
Patients aborting	25*
Multiple pregnancies	20**
Twins	15**
Three or more conceptions	5**
Fetal abnormalities	1.7**
Hyperstimulation syndrome	1.3

*Based on total pregnancies
**Based on total deliveries

Results by diagnosis group are summarized in Table 3 (these values include patients who were treated with other than the present recommended dosage regime): [1]

Table 3: Effectiveness of Menotropins

	% Pts Ovul.	% Pts Preg.	% Abort.	% Multi Preg.	% Twins	% 3 or More Concep.	% HyperstimSyndr.
Primary Amenorrhea	62	22	14	25	25	0	0
Secondary Amenorrhea	61	28	24	28	18	10	1.9
Secondary Amenorrhea w/ Galactorrhea	77	42	21	41	31	10	1.2
Polycystic Ovaries	76	26	39	17	17	0	1.1
Anovulatory Cycles	77	24	15	14	9	5	2
Miscellaneous	83	20	36	2	2	0	0.1

Efficacy results, based on intent to treat analyses, for two randomized, active controlled, multi-centre studies in IVF and OI sponsored by Ferring Pharmaceuticals Inc. are summarized in Tables 4 and 5 respectively.

Clinical Trials

Efficacy results from a clinical trial in *in vitro* fertilization (IVF) patients and a clinical trial in ovulation induction (OI) in anovulatory and oligoovulatory patients are summarized in Tables 4 and 5 respectively. Both studies were multicentre, active control, randomized, parallel group designs. In addition, all patients in both studies underwent pituitary suppression with a GnRH agonist before starting treatment with Repronex or the control

therapy. The IVF study evaluated 186 patients (125 patients receiving Repronex). The patients treated with Repronex received 225 IU Repronex daily for 5 days. This was followed by individual titration of the dose from 75 IU to 450 IU daily based on ultrasound and estradiol (E_2) levels. The total duration of dosing did not exceed twelve days. The OI study evaluated 108 patients (72 patients received Repronex). The patients treated with Repronex received 150 IU Repronex daily for five days. This was followed by individual titration of the dose from 75 to 450 IU daily based on ultrasound and estradiol (E_2) levels. The total duration of dosing did not exceed twelve days.

Repronex, given either subcutaneously or intramuscularly, was well tolerated when used to stimulate follicle development, and most adverse events were unrelated to study drugs. In the ovulation induction trial, the three serious adverse events were OHHS (a well documented side effect of gonadotropins), pelvic pain, or pelvic infection. In the trial of patients undergoing *in-vitro* fertilization, the events were also unrelated to study drugs, and serious adverse events were either OHSS or ectopic pregnancies.

Table 4: Efficacy Outcomes by Treatment Group for IVF (one cycle of treatment)

Parameter	Repronex IM N=65	Repronex SC N=60
Total oocytes retrieved	13.6	12.7
Mature oocytes retrieved	9.4	8.6
Pts w/oocyte retrieval (%)	61 (93.8)	55 (91.7)
Pts w/embryo transfer (%)	58 (89.2)	51 (85.0)
Pts w/chemical pregnancy (%)	31 (47.7)	35 (58.3)
Pts w/clinical pregnancy (%)	25 (38.5)	30 (50.0)
Pts w/continuing pregnancy (%)	24 (36.9)[1]	29 (48.3)[2]
Pts w/live births (%)	22 (33.8)[3]	25 (41.7

1. Continuing pregnancies included 14 single, 7 twins, and 3 triplet regnancies.
2. Continuing pregnancies included 14 single, 9 twins, 3 triplets and 3 quadruplet pregnancies.
3. Total of 34 live births. One spontaneous abortion. The follow-up data is not available for one patient.
4. Total of 39 live births. Two spontaneous abortions. The follow-up data is not available for two patients.

Table 5: Efficacy Outcomes by Treatment Groups in Ovulation Induction (one cycle of treatment)

Parameter	Repronex IM	Repronex SC
	N=36	**N=36**
Ovulation (%)	23 (63.9)	25 (69.4)
Received hCG (%)	25 (69.4)	27 (75.0)
Mean peak serum E2 (SD)	1158.5 (742.3)	1452.6* (1270.6)
Chemical pregnancy (%)	4 (11.1)	11 (30.6)
Clinical pregnancy (%)	4 (11.1)	6 (16.7)
Continuing pregnancy (%)	4 (11.1)[1]	6 (16.7)[2]
Pts w/live births (%)	4 (11.1)[3]	4 (11.1)[4]

* Fisher=s Exact/Chi-Squared Tests - significant for Repronex SC vs.

Repronex IM

1. Continuing pregnancies included 2 single and 2 triplet pregnancies.
2. Continuing pregnancies included 3 single, 1 twin and 2 quadruplet pregnancies.
3. Total 6 live births.
4. Total of 6 live births. One spontaneous abortion. The follow-up data is not available for one patient.

TOXICOLOGY

Menotropins were injected as a single IM dose of 35 IU/kg to rats and dog. This dose is ten times the highest clinical dose used in humans. There was no significant effect on mean arterial blood pressure, heart rate, cardiac output or ECG following this dose. [8, 9]

Anaphylaxis studies were also undertaken, where the menotropins were tested (35 IU/kg/day) against saline for a 12 day period, for their potential to cause anaphylaxis following IM administration in guinea pigs. Physical examinations and clinical observations showed no adverse effects from the injections of the menotropins. Sera from animals was tested, and all analyses were reported to be negative, with the exception of one animal which was positive for simian virus 5 (SV5) one day after receipt and again at the end of the study. Titers from guinea pigs given menotropins were greater than those of controls. The presence of titer of antibody indicates that the animal would have the propensity for anaphylaxis upon challenge with the same antigen. However there is no correlation between magnitude of titer and magnitude of anaphylactic response because many different inhibitors (not measured) of anaphylaxis are present in the host.[10]

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