

Fertinex®

(urofollitropin for injection, purified)

FOR SUBCUTANEOUS INJECTION

Serono

DESCRIPTION

Fertinex® (urofollitropin for injection, purified) is a preparation of highly purified Follicle Stimulating Hormone (FSH) extracted from the urine of post-menopausal women. Purification is by immunoaffinity chromatography using murine monoclonal antibody to human FSH. The purification process results in a consistent FSH isoform profile, significantly enhanced specific activity (8,500-13,500 IU FSH/mg protein), and a highly purified preparation. Each ampule of Fertinex® contains either 75 IU or 150 IU of highly purified FSH and 10 mg lactose in a sterile, lyophilized form. If required, pH is adjusted with 0.1M hydrochloric acid and/or 0.1M sodium hydroxide. Fertinex® is administered by subcutaneous injection. Fertinex® contains an acidic, water soluble glycoprotein biologically standardized for FSH gonadotropin activity in terms of the Second International Reference Preparation for Human Menopausal Gonadotropins established in September, 1964 by the Expert Committee on Biological Standards of the World Health Organization. Negligible amounts (≤ 0.1 IU LH/1000 IU FSH) of luteinizing hormone (LH) activity are contained in Fertinex®.

Therapeutic Class: Infertility.

CLINICAL PHARMACOLOGY

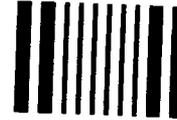
Fertinex® (urofollitropin for injection, purified) stimulates ovarian follicular growth in women who do not have primary ovarian failure. FSH, the active component of Fertinex®, is the primary hormone responsible for follicular recruitment and development. In order to effect final maturation of the follicle and ovulation in the absence of an endogenous LH surge, human chorionic gonadotropin (hCG) must be given following the administration of Fertinex® when monitoring of the patient indicates that sufficient follicular development has occurred. There may be a degree of interpatient variability in response to FSH administration.

Pharmacokinetics:

In a comparative, single-dose, double-blind, double-dummy, randomized, cross-over study, Fertinex® administered subcutaneously demonstrated a similar pharmacokinetic profile to urofollitropin and Fertinex® administered intramuscularly. No significant differences were found between the treatment groups in AUC/dose and CMAX/dose parameters. A variability in TMAX was observed. Subcutaneous administration of Fertinex® led to a slower absorption rate resulting in a later TMAX (15±7h) than following IM administration of either Fertinex® (10±4h) or urofollitropin (9±4h).

Plasma inhibin levels were measured as a pharmacodynamic marker of FSH activity. The inhibin concentration-time profile of inhibin following Fertinex® administered subcutaneously was found to be similar to that following urofollitropin and Fertinex® administered intramuscularly.

Special Populations: Safety and efficacy of Fertinex® in renal or hepatic insufficiency have not been established.



Drug-Drug Interactions: No clinically significant drug-drug interactions have been reported (see PRECAUTIONS).

Clinical Studies:

1. Ovulation Induction:

The safety and efficacy of Fertinex® administered subcutaneously vs. urofollitropin administered intramuscularly for ovulation induction was assessed in a phase III, open-label, randomized, comparative, multicenter study in oligo-ovulatory infertile women who failed to ovulate or conceive following adequate clomiphene citrate therapy. The purpose of the study was to demonstrate that Fertinex®, a highly purified follicle stimulating hormone (FSH) administered subcutaneously, is clinically not different in terms of safety and efficacy from urofollitropin administered intramuscularly. The principal efficacy parameters recorded were serum estradiol levels, follicular growth, ovulation rate and pregnancy rate. Two hundred eleven patients entered treatment, of whom 108 received Fertinex® and 103 received urofollitropin. Overall, two hundred and four patients (491 cycles) were considered evaluable. There were no differences between the Fertinex® administered subcutaneously and the urofollitropin intramuscular treatment groups in serum estradiol levels and follicular growth (follicle number and size) on the day of human chorionic gonadotropin (hCG) administration, nor were there any differences between the treatment groups in ovulation rates or pregnancy rates per patient.

The results of safety and efficacy with Fertinex® administered subcutaneously for ovulation induction in oligo-ovulatory infertile women are summarized below:

Cumulative Patient Ovulation Rates:

The cumulative patient ovulation rate by cycle is presented for the 102 evaluable patients with documentation of ovulatory status in at least one cycle:

Cycle 1	83%
Cycle 2	97%
Cycle 3	100%

Cumulative Patient Pregnancy Rates:

The cumulative patient pregnancy rate by cycle is presented for 86 evaluable patients who received hCG:

Cycle 1	14%
Cycle 2	21%
Cycle 3	29%
Patients Aborting*	8%
Multiple Births*	21%
Severe Hyperstimulation Syndrome**	0%

* Based upon 25 evaluable clinical pregnancies

** Based upon 108 patients and 266 cycles evaluable for safety

2. Assisted Reproductive Technologies (ART):

The safety and efficacy of Fertinex® administered subcutaneously for Assisted Reproductive Technologies (ART) were assessed in a phase III, multicenter, non-comparative, clinical trial in ovulatory infertile women undergoing stimulation of multiple follicular development for In Vitro Fertilization and Embryo Transfer (IVF/ET) after pituitary down-regulation with a GnRH agonist. The initial and maximal doses of Fertinex® were 225 and 450 IU, respectively. The principal parameters recorded were serum estradiol on day of

hCG administration, the number and maturity of retrieved oocytes, drug therapy and duration, and clinical pregnancy rate per initiated cycle and per retrieval. One hundred and thirty-nine patients were enrolled in the study; 135 patients were treated with Fertinex® and 122 patients were considered evaluable for efficacy. The results listed below represent mean data of 118 evaluable patients who received hCG in the 10 study centers:

Total number of oocytes recovered	8.4
Mature oocytes recovered	5.9
Maximum serum E2, day hCG (pg/mL)	1682
Total number of ampules (75 IU)	36
Treatment duration (days)	11.5
Clinical pregnancy attempt	23% (0-60)*
Clinical pregnancy transfer	27% (0-60)*

* reflects range across centers

INDICATIONS AND USAGE

Fertinex® (urofollitropin for injection, purified) and hCG given in a sequential manner are indicated for the stimulation of follicular recruitment and development and the induction of ovulation in patients with polycystic ovary syndrome and infertility, who have failed to respond or conceive following adequate clomiphene citrate therapy.

Fertinex® and hCG may also be used to stimulate the development of multiple follicles in ovulatory patients undergoing Assisted Reproductive Technologies (ART) such as in vitro fertilization.

Selection of Patients:

1. Before treatment with Fertinex® (urofollitropin for injection, purified) is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. This should include an assessment of pelvic anatomy. Patients with tubal obstruction should receive Fertinex® only if enrolled in an in vitro fertilization program.
2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.
3. Careful examination should be made to rule out the presence of early pregnancy.
4. Patients in late reproductive life have a greater predisposition to endometrial carcinoma as well as a higher incidence of anovulatory disorders. A thorough diagnostic examination should always be performed before starting Fertinex® therapy in such patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities.
5. Evaluation of the partner's fertility potential should be included in the workup.

CONTRAINDICATIONS

Fertinex® (urofollitropin for injection, purified) is contraindicated in women who exhibit:

1. High levels of FSH indicating primary ovarian failure.
2. Uncontrolled thyroid or adrenal dysfunction.
3. An organic intracranial lesion such as a pituitary tumor.
4. The presence of any cause of infertility other than anovulation, as stated in the "Indications" unless they are candidates for Assisted Reproductive Technologies.
5. Abnormal bleeding of undetermined origin (see "Selection of Patients").
6. Ovarian cysts or enlargement of undetermined origin.

7. Prior hypersensitivity to urofollitropin.

Fertinex® is also contraindicated in women who are pregnant and may cause fetal harm when administered to a pregnant woman. There are limited human data on the effects of Fertinex® when administered during pregnancy.

WARNINGS

Fertinex® (urofollitropin for injection, purified) should only be used by physicians who are thoroughly familiar with infertility problems and their management. It is a potent gonadotropic substance capable of causing mild to severe adverse reactions. Therefore, the lowest dose consistent with the expectation of good results should be used. 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"). Safe and effective use of Fertinex® requires monitoring of ovarian response with serum estradiol and vaginal ultrasound, on a regular basis.

Overstimulation of the Ovary During Fertinex® (urofollitropin for injection, purified) therapy:

Ovarian Enlargement: Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain occurs in approximately 20% of those treated with urofollitropin and hCG, and generally regresses without treatment within two or three weeks. Careful monitoring of ovarian response can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of Fertinex® 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. Severe OHSS may progress rapidly (within 24 hours to several days) 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 Ovarian Hyperstimulation Syndrome (OHSS).

Severe OHSS occurred in approximately 6.0% of patients treated with urofollitropin therapy in the initial clinical trials, in patients treated for anovulation due to polycystic ovarian syndrome. In these studies, prospective monitoring of ovarian response using serum estradiol determination or ultrasonographic visualizations was not routinely employed. In more recent clinical trials in oligo-anovulatory and infertile women in which both estradiol and ultrasound measurements were utilized to monitor follicular development, the incidence of severe OHSS was 0.6%. During studies for in vitro fertilization, four cases of OHSS were reported following 1,586 treatment cycles (0.25%). OHSS may be

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 must be withheld.

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

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

Pulmonary and Vascular Complications: The following paragraph describes serious medical events reported following gonadotropin therapy. 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. Intravascular thrombosis and embolism 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: Reports of multiple births have been associated with urofollitropin-hCG treatment, including triplet and quintuplet gestations. In clinical studies with Fertinex[®] 79.2% of the pregnancies following ovulation induction therapy resulted in single births and 20.8% in multiple births. The risk of multiple births in patients undergoing ART procedures is related to the number of embryos replaced. The patient and her partner should be advised of the potential risk of multiple births before starting treatment.

PRECAUTIONS

General: Careful attention should be given to diagnosis in candidates for Fertinex[®] (urofollitropin for injection, purified) therapy (see "Indications and Usage/Selection of Patients").

Information for Patients: Prior to the therapy with Fertinex[®], patients should be informed of the duration of treatment and monitoring of their condition that will be required. Possible adverse reactions (see "Adverse Reactions") and the risk of multiple births should also be discussed.

Laboratory Tests: In most instances, treatment with Fertinex[®] results only in follicular recruitment and development. In order to effect ovulation in the absence of an endogenous LH surge, hCG must be given following the administration of Fertinex[®] when monitoring of the patient indicates that sufficient follicular development has occurred. This may be estimated by serum estradiol and vaginal ultrasound. The combination of ultrasound and estradiol is useful for monitoring the development of follicles, timing hCG administration, as well as for detecting ovarian enlargement and minimizing the risk of the Ovarian Hyperstimulation Syndrome and multiple gestation. It is recommended that the number of growing follicles be confirmed using ultrasonography because plasma estrogen alone does not give an indication of the size or number of follicles.

The clinical confirmation of ovulation, with the exception of pregnancy,

is obtained by direct and indirect indices of progesterone production. The indices generally used are:

1. A rise in basal body temperature,
2. Increase in serum progesterone, and
3. 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:

1. Fluid in the cul-de-sac,
2. Ovarian stigmata,
3. Collapsed follicle, and
4. Secretory endometrium.

Accurate interpretation of the indices of follicular development and maturation as well as the determination of ovulation require a physician who is experienced in the interpretation of these tests.

Drug Interactions: No clinically significant drug/drug or drug/food interactions have been reported during Fertinex[®] therapy.

Carcinogenesis and Mutagenesis: Carcinogenicity and mutagenicity studies have not been performed.

Pregnancy Category X: 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 Fertinex[®] is administered to a nursing woman.

ADVERSE REACTIONS

The following adverse reactions reported during urofollitropin therapy are listed in decreasing order of potential severity:

1. Pulmonary and vascular complications (see "Warnings"),
2. Ovarian Hyperstimulation Syndrome (see "Warnings"),
3. Adnexal torsion (as a complication of ovarian enlargement),
4. Mild to moderate ovarian enlargement,
5. Abdominal pain,
6. Sensitivity to urofollitropin (Febrile reactions which may be accompanied by chills, musculoskeletal aches, joint pains, malaise, headache, and fatigue have occurred after the administration of urofollitropin. It is not clear whether or not these were pyrogenic responses or possible allergic reactions.)
7. Ovarian cysts,
8. Gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal cramps, bloating),
9. Pain, rash, swelling, and/or irritation at the site of injection,
10. Breast tenderness,
11. Headache,
12. Dermatological symptoms (dry skin, body rash, hair loss, hives)
13. Hemoperitoneum has been reported during menotropins therapy and, therefore, may also occur during urofollitropin therapy.
14. 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.

The following medical events have been reported subsequent to pregnancies resulting from urofollitropin therapy:

1. Ectopic Pregnancy

2. Congenital abnormalities

(Three incidents of chromosomal abnormalities and four birth defects have been reported following urofollitropin-hCG or urofollitropin, Pergonal[®] (menotropins for injection, USP)-hCG therapy in clinical trials for stimulation prior to in vitro fertilization. The aborted pregnancies included one Trisomy 13, one Trisomy 18, and one fetus with multiple congenital anomalies (hydrocephaly, omphalocele, and meningocele). One meningocele, one external ear defect, one dislocated hip and ankle, and one dilated cardiomyopathy in presence of maternal Systemic Lupus Erythematosus were reported. None of these events were thought to be drug-related. The incidence does not exceed that found in the general population).

DRUG ABUSE AND DEPENDENCE

There have been no reports of abuse or dependence with Fertinex[®] (urofollitropin for injection, purified).

OVERDOSAGE

Aside from possible ovarian hyperstimulation and multiple gestations (see "Warnings"), little is known concerning the consequences of acute overdosage with Fertinex[®] (urofollitropin for injection, purified).

DOSAGE AND ADMINISTRATION

Dosage:

Polycystic Ovary Syndrome: The dose of Fertinex[®] (urofollitropin for injection, purified) to stimulate development of the follicle must be individualized for each patient.

The lowest dose consistent with the expectation of good results should be used. Over the course of treatment, doses of Fertinex[®] may range between 75 IU to 300 IU per day depending on the individual patient response. Fertinex[®] should be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography. A response is generally evident after 5 to 7 days. Subsequent monitoring intervals should be based on individual patient response.

It is recommended that the initial dose of the first cycle be 75 IU of Fertinex[®] per day, ADMINISTERED SUBCUTANEOUSLY. An adjustment in dose may be considered after 5 to 7 days. An additional dose adjustment may also be considered based on individual patient response. The dose should not be increased more than twice in any cycle or by more than one ampule (75 IU) per adjustment. To complete follicular development and effect ovulation in the absence of an endogenous LH surge, hCG, 5,000 U to 10,000 U, should be given 1 day after the last dose of Fertinex[®]. Human chorionic gonadotropin should be withheld if the serum estradiol is greater than 2,000 pg/mL. If the ovaries are abnormally enlarged or abdominal pain occurs, Fertinex[®] treatment should be discontinued, hCG should not be administered, and the patient should be advised not to have intercourse; this will reduce the chance of development of the Ovarian Hyperstimulation Syndrome and, should spontaneous ovulation occur, reduce the chance of multiple gestation. A follow-up visit should be conducted in the luteal phase.

The initial dose administered in the subsequent cycles should be individualized for each patient based on her response in the preceding cycle. Doses larger than 300 IU of FSH per day are not routinely recommended. As in the initial cycle, 5,000 U to 10,000 U of hCG must be given 1 day after the last dose of Fertinex[®] to complete follicular

development and induce ovulation. The precautions described above should be followed to minimize the chance of development of the Ovarian Hyperstimulation Syndrome.

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 ensure insemination. In light of the 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 Fertinex[®].

Assisted Reproductive Technologies: As in the treatment of patients with polycystic ovary syndrome, the dose of Fertinex[®] to stimulate development of the follicle must be individualized for each patient. For Assisted Reproductive Technologies, therapy with Fertinex[®] should be initiated in the early follicular phase (cycle day 2 or 3) at a dose of 150 IU per day, until sufficient follicular development is attained. In most cases, therapy should not exceed ten days.

Administration: Dissolve the contents of one or more ampules of Fertinex[®] in one-half to one mL of sterile saline (concentration should not exceed 225 IU/0.5 mL) and ADMINISTER SUBCUTANEOUSLY immediately. Any unused reconstituted material should be discarded. Parenteral drug products should be inspected visually, for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Fertinex[®] (urofollitropin for injection, purified) is supplied in a sterile, lyophilized form as a white to off-white powder or pellet in ampules containing 75 IU or 150 IU FSH activity. The following package combinations are available:

- 1 ampule 75 IU Fertinex[®] and 1 ampule 2 mL Sodium Chloride Injection (USP), NDC 44087-7075-1
- 1 ampule 150 IU Fertinex[®] and 1 ampule 2 mL Sodium Chloride Injection (USP), NDC 44087-7150-1
- 10 ampules 75 IU Fertinex[®] and 10 ampules 2 mL Sodium Chloride Injection (USP), NDC 44087-7075-3
- 100 ampules 75 IU Fertinex[®] and 100 ampules 2 mL Sodium Chloride Injection (USP), NDC 44087-7075-4

Lyophilized powder may be stored refrigerated or at room temperature (3°-25°C/37°-77°F). Protect from light. Use immediately after reconstitution. Discard unused material.

Rx only

Manufactured for: SERONO LABORATORIES, INC.,
Randolph, MA 02368 U.S.A.
by: Laboratoires Serono SA, Aubonne, Switzerland

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