

Pergonal® (menotropins for injection, USP) FOR INTRAMUSCULAR INJECTION

DESCRIPTION

Pergonal® (menotropins for injection, USP) is a purified preparation of gonadotropins extracted from the urine of postmenopausal women. Each ampoule of Pergonal contains 75 IU or 150 IU of follicle stimulating hormone (FSH) activity and 75 IU or 150 IU of luteinizing hormone (LH) activity, respectively, plus 10 mg lactose in a sterile, lyophilized form. Human Chorionic Gonadotropin (hCG), a naturally occurring hormone in postmenopausal urine, is detected in Pergonal. Pergonal is administered by intramuscular injection.

Pergonal is biologically standardized for FSH and LH (ICSH) gonadotropin activities 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. Both FSH and LH are glycoproteins that are acidic and water soluble therapeutic class. Infertility.

Clinical Pharmacology

Women: Pergonal administered for seven to twelve days produces ovarian follicular growth in women who do not have primary ovarian failure. Treatment with Pergonal 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 Pergonal when clinical assessment of the patient indicates that sufficient follicular maturation has occurred.

Men: Pergonal administered concomitantly with human chorionic gonadotropin (hCG) for at least three months induces spermatogenesis in men with primary or secondary pituitary hypofunction who have achieved adequate masculinization with prior hCG therapy.

Indications and Usage

Women: Pergonal and hCG given in a sequential manner are indicated for the induction of ovulation and pregnancy in the anovulatory infertile patient in whom the cause of anovulation is functional and is not due to primary ovarian failure.

Pergonal and hCG may also be used to stimulate the development of multiple follicles in ovulatory patients participating in an in vitro fertilization program.

Men: Pergonal with concomitant hCG is indicated for the stimulation of spermatogenesis in men who have primary or secondary hypogonadotropic hypogonadism.

Pergonal with concomitant hCG has proven effective in inducing spermatogenesis in men with primary hypogonadotropic hypogonadism due to a congenital factor or prepubertal hypophysism and in men with secondary hypogonadotropic hypogonadism due to hypophysectomy, craniopharyngioma, cerebral aneurysm or chromophobe adenoma.

Selection of Patients

Women

1. Before treatment with Pergonal 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 urinary) progesterone, urinary pregnandiol and endometrial biopsy. Patients with tubal pathology should receive Pergonal 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 an early pregnancy.
4. Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory disorders. Cervical dilation and curettage should always be done for diagnosis before starting Pergonal therapy in such patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities.
5. Evaluation of the husband's fertility potential should be included in the workup.

Men: Patient selection should be made based on a documented lack of pituitary function. Prior to hormonal therapy, these patients will have low testosterone levels and low or absent gonadotropin levels. Patients with primary hypogonadotropic hypogonadism will have a subnormal development of masculinization, and those with secondary hypogonadotropic hypogonadism will have decreased masculinization.

Contraindications

- Women:** Pergonal is contraindicated in women who have
1. A high FSH level indicating primary ovarian failure.
 2. Uncontrolled thyroid and adrenal dysfunction.
 3. An organic intracranial lesion such as a pituitary tumor.
 4. The presence of any cause of infertility other than anovulation, unless they are candidates for in vitro fertilization.
 5. Abnormal bleeding of undetermined origin.
 6. Ovarian cysts or enlargement not due to polycystic ovary syndrome.
 7. Prior hypersensitivity to menotropins.
 8. Pergonal is 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 Pergonal when administered during pregnancy.

Men

Pergonal is contraindicated in men who have

1. Normal gonadotropin levels indicating normal pituitary function.
2. Elevated gonadotropin levels indicating primary testicular failure.
3. Infertility disorders other than hypogonadotropic hypogonadism.

Warnings

Pergonal is a drug that should only be used by physicians who are thoroughly familiar with infertility problems. It is a potent gonadotropin substance capable of causing mild to severe adverse reactions in women. Gonadotropin therapy requires a certain degree of commitment by physicians and supportive health professionals, and it also requires the availability of appropriate monitoring facilities (see Precautions - Laboratory Tests) in the patients who are used with a great deal of care.

Overstimulation of the Ovary During Pergonal Therapy

Ovarian enlargement, mild to moderate, and/or ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain, occurs in approximately 20% of those treated with Pergonal and hCG, and generally regresses without the patient's aid within two or three weeks. In order to minimize the hazard associated with the occasional abnormal ovarian enlargement which may occur with Pergonal and hCG therapy, the lowest dose consistent with expectations 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 Pergonal 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) is a medical event distinct from ovarian enlargement which may occur with Pergonal and hCG therapy. It is a clinical entity characterized by abdominal distension, weight gain, and/or fluid retention, which is accompanied by an apparent increase in the number of follicles and/or the number of follicles which are aspirated. The early warning signs of OHSS are abdominal distension, weight gain, nausea, vomiting, and/or diarrhea. These symptoms have also been reported in

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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, changes in 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 doses are administered and in 1.3% of patients when higher than recommended doses are administered. 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 ten 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 antibiotics if needed. The phenomenon of hemoconcentration associated with fluid loss into the peritoneal cavity, pleural cavity, and the pericardial cavity has been noted to occur and should be thoroughly assessed at 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 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 thromboembolism, pleural effusion, 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 isotonic fluids, electrolytes, and human serum albumin.

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 Pergonal 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: Data from a clinical trial revealed the following results regarding multiple births: Of the pregnancies following therapy with Pergonal and hCG, 80% resulted in single births, 15% in twins, and 5% of the total pregnancies resulted in three or more concepts. The patient and her husband should be advised of the frequency and potential hazards of multiple gestation before starting treatment.

Hypersensitivity/Anaphylactic Reactions: Serious hypersensitivity/anaphylactic reactions associated with Pergonal 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 Pergonal therapy (see Indications and Usage - Selection of Patients).

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

Laboratory Tests

Women: Treatment for Induction of Ovulation. In most instances, treatment with Pergonal results only in follicular growth and maturation. In order to effect ovulation, hCG must be given following the administration of Pergonal 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 ultrasonographic visualization during the growth and development of follicles (forming a Graafian follicle) as well as measuring the risk of the Ovarian Hyperstimulation Syndrome and multiple gestation.

Other clinical parameters which may have potential use for monitoring response to therapy include:

1. Changes in the vaginal cytology.
2. Appearance and volume of the cervical mucus.
3. Serum estradiol.
4. Serum progesterone.
5. The above clinical indices provide an indirect estimate of the estrogenic effect upon the target organ, and therefore should only be used in conjunction 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:

1. A rise in basal body temperature.
2. Increase in serum progesterone.
3. Menstruation following the shift in basal body temperature.
4. When used in conjunction with indices of progesterone production, serial pelvic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation includes the following:
 - a. A rise in basal body temperature.
 - b. Ovarian enlargement.
 - c. Disappearance of the corpus luteum.

The above clinical parameters of the ovulation cycle should be monitored

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Follicular maturation and ovulation, it cannot be overemphasized that the physician should choose tests with which he/she is thoroughly familiar.

Drug Interactions: No clinically significant drug/drug or drug/food adverse interactions have been reported during Pergonal therapy.

Carcinogenesis and Mutagenesis: Long-term toxicology studies in animals have not been performed to evaluate the carcinogenic potential of Pergonal.

Pregnancy: Pregnancy Category X. See "Contraindications" section.

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

Adverse Reactions

- Women:** The following adverse reactions reported during Pergonal therapy are listed in decreasing order of potential severity:
1. Pulmonary and vascular complications (see "Warnings").
 2. Ovarian Hyperstimulation Syndrome (see "Warnings").
 3. Hemoperitoneum.
 4. Adnexal torsion (as a complication of ovarian enlargement).
 5. Mild to moderate ovarian enlargement.
 6. Ovarian cysts.
 7. Abdominal pain.
 8. Sensitivity to Pergonal (febrile reactions suggestive of allergic response have been reported following the administration of Pergonal). Reports of flu-like symptoms including fever, chills, musculoskeletal aches, joint pains, nausea, headaches, and malaise have also been reported.
 9. Gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal cramps, bloating).
 10. Pain, rash, swelling and/or irritation at the site of injection.
 11. Body rashes.
 12. Dizziness, tachycardia, dyspnea, tachypnea.

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

1. Ectopic pregnancy.
2. Congenital abnormalities. From a study of 287 completed pregnancies following Pergonal-hCG therapy, live congenital anomalies consisting of imperforate anus, aplasia of the sigmoid colon, third degree hypospadias, cecocolic fistula, bifid scrotum, and polydactyly were reported in 1.7%. One infant had multiple congenital anomalies consisting of imperforate anus, aplasia of the sigmoid colon, 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 ectropion 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 reported.

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.

Men

1. Gynecomastia may occur occasionally during Pergonal-hCG therapy. This is a known effect of hCG treatment.
2. Erythrocytosis (hct 50%, hgb 17.8 g%) was recorded in one patient.

Drug Abuse and Dependence

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

Overdosage

Aside from possible ovarian hyperstimulation (see "Warnings"), little is known concerning the consequences of acute overdosage with Pergonal.

Dosage and Administration

Women

1. Dosage:

The dose of Pergonal to produce maturation of the follicle must be individualized for each patient. It is recommended that the initial dose to any patient be 75 IU of FSH/LH per day. ADMINISTERED INTRAMUSCULARLY for seven to twelve days followed by hCG 5,000 U to 10,000 U, one day after the last dose of Pergonal. Administration of Pergonal should not exceed 12 days in a single course of therapy. The patient should be treated until indices of estrogenic activity, as indicated under "Precautions" above, are equivalent to or greater than those of the normal individual. If serum or urinary estradiol determinations or ultrasonographic visualizations are available, they may be used as a guide to therapy. If the ovaries are abnormally enlarged or the Ovarian Hyperstimulation Syndrome is present, hCG should not be administered in this course of therapy. This will reduce the chances of development of the Ovarian Hyperstimulation Syndrome. If there is evidence of ovulation but no pregnancy, repeat this dosage regime for at least two more courses before increasing the dose of Pergonal to 150 IU of FSH/LH per day for seven to twelve days. As before, this dose should be followed by Pergonal's dose of 150 IU of FSH/LH per day after the last dose of Pergonal. A effective dose, especially for in vitro fertilization. If evidence of ovulation is present, but pregnancy does not ensue, repeat the same dose for two more courses. Doses larger than this are not routinely recommended.

During treatment with both Pergonal and hCG and during a two week post-treatment period, patients should be examined at least every other day for signs of excessive ovarian stimulation. It is recommended that Pergonal administration be stopped if the ovaries become abnormally enlarged or abdominal pain occurs. Most often, the Ovarian Hyperstimulation Syndrome occurs after treatment has been discontinued. Patients should be followed for at least two weeks after hCG administration.

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 preovulatory 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 should not use Pergonal.

Administration

Dissolve the contents of one ampoule of Pergonal in one to two ml of sterile saline and ADMINISTER INTRAMUSCULARLY immediately. Any unused or wasted material should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Men

1. Dosage:

Prior to treatment with Pergonal and hCG, pretreatment with hCG alpha 1,500 U three times a week is required. Treatment should continue for a period sufficient to achieve serum testosterone levels within the normal range and masculinization as judged by the appearance of secondary sex characteristics. Such pretreatment may require four to six months, then the recommended dose of Pergonal is 75 IU FSH/LH ADMINISTERED INTRAMUSCULARLY, three times a week and the recommended dose of hCG is 2,000 U twice a week. Therapy should be carried on for a minimum of four to six months to insure detecting spermatogenesis in the ejaculate. Takes 74 - 84 days in the human male for germ cells to reach the spermatozoa stage.

If the patient has not responded with evidence of increased sperm and gonads after one to four months of therapy, the treatment should continue with 75 IU FSH/LH three times a week, or the dose can be increased to 150 IU FSH/LH three times a week with the hCG dose unchanged.

2. Administration

Discuss the safety of the ampoule of Pergonal in the following manner: ADMINISTER INTRAMUSCULARLY immediately and

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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

Pergonal® 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/LH activity. The following package combinations are available:

- 1 ampule 75 IU Pergonal® and 1 ampule 2 ml Sodium Chloride Injection (USP), NDC 44087-0571-7
- 10 ampules 75 IU Pergonal® and 10 ampules 2 ml Sodium Chloride Injection (USP), NDC 44087-5075-3
- 1 ampule 150 IU Pergonal® and 1 ampule 2 ml Sodium Chloride Injection (USP), NDC 44087-5150-1

By biological assay, one IU of LH for the Second International Reference Preparation (2nd-IRP) for hMG is biologically equivalent to approximately 1/2 U of hCG.

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.

Clinical Studies

Women: The results of the clinical experience and effectiveness of the administration of Pergonal® 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.

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

*Based on total pregnancies

†Based on total deliveries

Results by diagnosis group are summarized below (these values include patients who were treated with other than the present recommended dosage regime):

	% Pts. Ovul.	% Pts Preg.	% Abort.	% Multi. Preg.	% Twins	% 3 or More Concepti	% Hyperstim. Syndr.
Primary							
Amenorrhea	62	22	14	25	25	0	0
Secondary							
Amenorrhea	61	28	24	28	18	10	1.9
Amen with 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	2.0
Miscellaneous	83	20	36	2	2	0	0.1

Men

Clinical results of the treatment of men with primary or secondary hypogonadotropic hypogonadism are as follows:

In the SeroCooperative study, with an adequate treatment period of 3 to 8 months, 60 of 70 men with primary hypogonadotropic hypogonadism and 8 of 11 men with secondary hypogonadotropic hypogonadism responded with mean increases in their sperm counts from less than 5 to 24 million spermatozoa per milliliter of ejaculate. Forty-one wives of 54 men with primary hypogonadotropic hypogonadism desiring offspring and 7 wives of men with secondary hypogonadotropic hypogonadism conceived. Patients treated with Pergonal® and hCG for less than 3 months or with Pergonal® alone did not respond to therapy.

A world-wide data search revealed that of 160 recorded pregnancies as the result of use of Pergonal®-hCG in men, there were 7 spontaneous abortions, one ectopic pregnancy and 3 congenital anomalies at birth (esophageal atresia in a female infant which was later corrected by surgery, unilateral cryptorchidism, inguinal hernia).

Caution: Federal law prohibits dispensing without prescription.

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