

# Male Pergonal® (hMG).

**The only therapy proven safe and effective in hypogonadotropic hypogonadism!**

Now, male Pergonal (human Menopausal Gonadotropin) is here.

Already in use in over 30 countries, it's available for the first time for males in the United States.

This represents a major breakthrough in the treatment of male subfertility. Pergonal (hMG), combined with human Chorionic Gonadotropin (Serono's Profasi® HP or other brand) is the only therapy for the enhancement and completion of spermatogenesis in hypogonadotropic hypogonadism associated with lowered levels of gonadotropins.

Infertile men can benefit from the same product that has been used successfully for nearly 20 years in the treatment of infertile women.

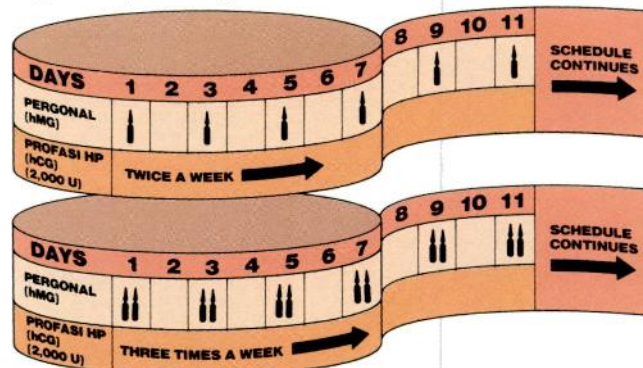
Male Pergonal (hMG). Now, it's here.

**Pergonal (hMG) and Profasi HP (hCG) provide complete replacement of pituitary function in the regulation of male gonadal activity.**

Steroidogenic and spermatogenic male gonadal functions are controlled by two pituitary hormones: LH and FSH. Both gonadotropins are needed for testosterone production by interstitial cells and for spermatogenic activity of seminiferous tubules.

Male infertility attributable to deficiency in sperm production associated with deficiency in gonadotropin levels can be successfully treated with human gonadotropins according to the following schedules.

**Schedule 1** (following pretreatment with Profasi HP or other brand of hCG): One ampule every other day.



**Schedule 2** (following pretreatment with Profasi HP or other brand of hCG): Two ampules every other day.

EFFICACY AND SAFETY OF hCG/hMG (PERGONAL) TREATMENT IN MEN WITH HYPOGONADOTROPIC HYPOGONADISM.			
SOURCE	NUMBER OF PATIENTS	INCREASED SPERMATOGENESIS	CONCEPTION ATTAINED/ DESIRED
CLINICAL TRIALS (17 INVESTIGATIONS)	76	66/76	47/60
PUBLICATIONS (12 REFERENCES)	45	38/45	21/26
<b>TOTAL</b>	<b>121</b>	<b>104/121 (86%)</b>	<b>68/86 (79%)</b>

Prior to concomitant therapy with Pergonal (hMG) and hCG, pretreatment with hCG alone (5,000 U three times weekly) is required for a minimum of 4 months or until testosterone levels are normalized.

Schedule 1 is indicated for milder forms, one ampule every other day. Should the dosage be inadequate, switch to Schedule 2, two ampules every other day.

Regardless of the schedule employed, treatment should be continued uninterrupted for 90-120 days; if results are inadequate, additional treatment cycles employing the same schedule may be administered. Pergonal (hMG) and Profasi HP (hCG), for intramuscular use, may be administered together in a single injection. Once expected results are obtained, maintenance treatment may be initiated with 1-2 Pergonal (hMG) ampules weekly.

Male Pergonal (hMG) is available through your pharmacy or by ordering directly from Serono Laboratories, Inc.

For more information, simply call us toll-free at 800/225-5185. In Massachusetts, 617/848-8404.

**Serono**

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Braintree, Massachusetts 02184

<sup>1</sup>Resulting from isolated FSH or FSH/LH deficiencies.

(Please consult full product information for Pergonal (hMG) and Profasi HP (hCG) before prescribing. Pergonal (hMG) product information can be found on the following page.)

## PERGONAL® (menotropins)

**DESCRIPTION** Pergonal® (menotropins) is a purified preparation of gonadotropins extracted from the urine of postmenopausal women. Each ampule of Pergonal® contains 75 I.U. of follicle-stimulating hormone (FSH) activity and 75 I.U. of luteinizing hormone (LH) activity plus 10 mg lactose in a sterile, lyophilized form.

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.

**ACTIONS WOMEN:** Pergonal® administered for nine 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, hCG (human chorionic gonadotropin) 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 WOMEN:** Pergonal® and human chorionic gonadotropin (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.

**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 hypophysectomy 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. 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 urinary pregnandiol, and endometrial biopsy. 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® (menotropins) therapy in such patients. 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:** 1. A high gonadotropin level indicating primary ovarian failure. 2. The presence of overt 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, as stated in the indications. 5. In patients with abnormal bleeding of undetermined origin. 6. In patients with ovarian cysts or enlargement not due to polycystic ovary syndrome. 7. Pregnancy.

**MEN:** 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 gonadotropic substance capable of causing mild to severe adverse reactions in women. In female patients it must be used with a great deal of care.

### PRECAUTIONS WOMEN:

1. **Diagnosis Prior to Therapy** Careful attention should be given to diagnosis in candidates for Pergonal® therapy. (See sections headed "Indications" and "Selection of Patients.") 2. **Overstimulation of the Ovary During Pergonal® Therapy** In order to minimize the hazard associated with the occasional abnormal ovarian enlargement associated with Pergonal®-hCG therapy, the lowest dose consistent with expectation of good results should be used.

Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distention and/or abdominal pain occurs in approximately 20% of those treated with Pergonal® and hCG, and generally regresses without treatment within two or three weeks.

The hyperstimulation syndrome characterized by sudden ovarian enlargement accompanied by ascites with or without pain and/or pleural effusion occurs in approximately 0.4% of patients when the recommended dose is administered. In studies performed the overall incidence of the hyperstimulation syndrome was 1.3%.

If hyperstimulation occurs, treatment should be stopped and the patient hospitalized. The hyperstimulation syndrome develops rapidly over a period of three to four days and generally occurs during the two week period immediately following treatment. The phenomenon of hemoconcentration associated with fluid loss in the abdominal 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, and 5) urine specific gravity. These determinations are to be performed daily or more often if the need arises.

Treatment is primarily symptomatic and would consist primarily of bed rest, fluid and electrolyte replacement and analgesics if needed. The ascitic fluid should never be removed because of the potential danger of injury to the ovary.

Hemoperitoneum may occur from ruptured ovarian cysts. This is usually the result of pelvic examination. If this does

occur, and if bleeding becomes such that surgery is required, the conservative approach with partial resection of the enlarged ovary or ovaries is generally adequate.

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.

3. **Arterial Thromboembolism.** Arterial thromboembolism following Pergonal® (menotropins) and hCG therapy has been reported in two patients, one of whom died.<sup>1</sup>

4. **Multiple Births.** Of the pregnancies following therapy with Pergonal® and hCG, 80% have resulted in single births and 20% in multiple births, most of which have been twins. Fifteen percent of the total pregnancies resulted in twins, of which 93% were viable (78 surviving infants from 43 sets of twins). Five percent of the total pregnancies have resulted in three or more conceptuses, of which only 20% were viable (nine surviving infants from three sets of triplets, four surviving infants from four sets of quadruplets, and no surviving infants from four sets of quintuplets). The patient and her husband should be advised of the frequency and potential hazards of multiple pregnancy before starting treatment.

**ADVERSE REACTIONS WOMEN:** 1. Ovarian Enlargement. 2. Hyperstimulation Syndrome. 3. Hemoperitoneum. 4. Arterial Thromboembolism (see "Precautions" above). 5. Sensitivity to Pergonal®. Three patients experienced febrile reactions after the administration of Pergonal®. It is not clear whether or not these were pyrogenic responses or possibly allergic reactions.

6. **Defects at Birth:** From 287 completed pregnancies following Pergonal®-hCG therapy, five incidents of birth defects have been reported. One infant had multiple congenital anomalies consisting of imperforate anus, aplasia of the sigmoid colon, third degree hypospadias, cecovesical 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 ectropion of the bladder; and the fifth child had Down's syndrome. None of the investigators felt that these defects were drug-related.

**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 1 patient.

### DOSEAGE AND ADMINISTRATION FOR INTRAMUSCULAR ADMINISTRATION

**WOMEN:** 1. **Treatment for Induction of Ovulation.** Treatment with Pergonal® in most instances 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 is indirectly estimated by the estrogenic effect upon the target organs. These indices of estrogenic activity include: a) changes in the vaginal smear, b) appearance and volume of the cervical mucus, c) Spinnbarkeit, and d) ferning of the cervical mucus.

If available, the urinary excretion of estrogens is a more reliable index of follicular maturation. The clinical confirmation of ovulation, with the exception of pregnancy, is obtained by indirect indices of progesterone production. The indices most generally used are as follows: a) a rise in basal body temperature, b) change of the cervical mucus from a "fern" pattern to a "cellular" pattern, c) vaginal cytology characteristic of the luteal phase of the menstrual cycle, d) increase in urinary pregnandiol, and e) menstruation following the shift in basal body temperature.

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 is thoroughly familiar.

2. **Dosage of Pergonal®:** 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 should be 75 I.U. of FSH and 75 I.U. of LH (one ampule) per day. ADMINISTERED INTRAMUSCULARLY, for nine to twelve days followed by hCG, 10,000 I.U., one day after the last dose of Pergonal®. The hyperstimulation syndrome has never occurred with administration of 75 I.U. of FSH and 75 I.U. of LH (one ampule) per day for up to twelve days. Administration of Pergonal® should not exceed 12 days. The patient should be treated until indices of estrogenic activity, as indicated under Item 1 above, are equivalent to or greater than those of the normal individual. If urinary estrogen determinations are available, they may be useful as a guide to therapy. If the total estrogen excretion is less than 100 mcg/24 hours or the estril excretion is less than 50 mcg/24 hours prior to hCG administration, the hyperstimulation syndrome is less likely to occur. If the estrogen values are greater than this, it is not advisable to administer hCG because the hyperstimulation syndrome is more likely to occur.

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 hyperstimulation syndrome. If there is evidence of ovulation but no pregnancy repeat this dosage regimen for at least two more courses before increasing the dose of Pergonal® to 150 I.U. of FSH and 150 I.U. of LH (two ampules) per day for nine to twelve days. As before, this dose should be followed by 10,000 I.U. of hCG one day after the last dose of Pergonal®. 150 I.U. of FSH and 150 I.U. of LH (two ampules) of Pergonal® per day has proven to be the most effective dose. 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 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 of the ovarian hyperstimulation occurs after treatment has been discontinued and reaches its maximum at about seven to ten days post-ovulation. 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 progesterational 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® (menotropins).

3. **How to Administer Pergonal®:** Dissolve the contents of one ampule of Pergonal® in one to two ml. of sterile saline and ADMINISTER INTRAMUSCULARLY immediately. Any unused reconstituted material should be discarded.

**MEN:** 1. **Dosage of Pergonal®:** Prior to concomitant therapy with Pergonal® (hMG) and hCG, pretreatment with hCG alone (5,000 I.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 one ampule ADMINISTERED INTRAMUSCULARLY, three times a week and the recommended dose of hCG is 2,000 I.U. twice a week. Therapy should be carried on for a minimum of four more months to insure detecting spermatozoa in the ejaculate, as it takes 74 ± 4 days in the human male for germ cells to reach the spermatozoa stage.

In one clinical series consisting of nine patients, 4 patients produced 2 million sperm per ejaculate with a dosage of Pergonal® of 25 I.U. every other day concomitantly with 2,000 I.U. hCG three times a week. When 38 I.U. of Pergonal® every other day was administered, 7 of the 9 subjects produced at least 2 million sperm per ejaculate, and at the higher dose of 75 I.U. of Pergonal® every other day 8 of the 9 subjects were sperm positive at 2 million per ejaculate. In this series, Pergonal® was administered concomitantly with 2,000 I.U. hCG three times a week, after achievement of adequate masculinization with prior hCG therapy. The non-responder had a history of surgical orchiopexy to repair bilateral cryptorchidism at the age of 12, and this may have complicated the response of his testes to gonadotropin replacement. The results obtained in this series are in keeping with very recent studies quantitating the production rate of FSH in the human as approximately 30 or 40 I.U. a day.

If the patient has not responded with evidence of increased spermatogenesis at the end of four months, therapy treatment may continue with one ampule of Pergonal® three times a week, or the dose can be increased to two ampules (150 I.U. FSH and 150 I.U. LH) three times a week with the hCG dose unchanged.

2. **How to Administer Pergonal®:** Dissolve the contents of one ampule of Pergonal® in one to two ml. of sterile saline and ADMINISTER INTRAMUSCULARLY immediately. Any unused reconstituted material should be discarded.

**HOW SUPPLIED** Each ampule of Pergonal® (menotropins) contains 75 I.U. of FSH and 75 I.U. of LH (ICSH). By biological assay, one I.U. of LH for the Second International Reference Preparation (2nd-IRP) for hMG is biologically equivalent to approximately 1/2 I.U. of human chorionic gonadotropin (hCG).

**CLINICAL STUDIES WOMEN:** The results of the clinical experience and effectiveness of the administration of Pergonal® (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 regimen. The values for the presently recommended dosage regimen are essentially the same, except for the fact that the hyperstimulation syndrome has not occurred with administration of 75 I.U. of Pergonal® per day for 9 to 12 days and the incidence of the hyperstimulation syndrome with administration of 150 I.U. of Pergonal® per day for 9 to 12 days has not exceeded 0.4%.

	%
Patients ovulating	75
Patients pregnant	25
Patients aborting	25*
Multiple pregnancies	20†
Twins	1.5
Three or more conceptuses	1.7
Fetal abnormalities	5
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 regimen.)

	% Ovs.	% Pts Prog.	% Abort	% Mult. Preg.	% Twins	% 3 or More Con.	% Hyperstim. Syndr.
Primary Amenorrhea	62	22	14	25	25	0	0
Secondary Amenorrhea	61	28	24	28	18	10	1.9
Secondary Amenorrhea 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 Serozo Cooperative study, with an adequate treatment period of 3 to 8 months, 80 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).

**REFERENCES** 1. Mozes, M., Bogokowsky, H., Antebi, E., et al: Thromboembolic phenomena after ovarian stimulation with human gonadotropins. *Lancet* 2:1213-1215, 1965.

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