PRODUCT MONOGRAPH

PrGONAL-f® Pen

Follitropin alfa Injection

300 IU/0.48 mL, 450 IU/0.72 mL
and 900 IU/1.44 mL in prefilled pens filled by mass

Pharmaceutical Standard: Professed

Therapeutic Classification: Gonadotropin

EMD Serono, A Division of EMD Inc., Canada
2695 North Sheridan Way, Suite 200
Mississauga ON L5K 2N6
A Business of Merck KGaA, Darmstadt, Germany

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GONAL-f® Pen

Follitropin alfa Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Liquid in prefilled pen 300 IU/0.48 mL, 450 IU/0.72 mL, and 900 IU/1.44 mL	Not applicable. For a complete listing of the nonmedicinal ingredients see *DOSAGE FORMS, COMPOSITION AND PACKAGING*.

DESCRIPTION

GONAL-f® (follitropin alfa for injection) is a gonadotropin preparation of recombinant DNA origin. The active ingredient, recombinant human Follicle Stimulating Hormone (r-hFSH), is a human glycoprotein hormone which consists of two non-covalently linked, non-identical protein components designated as the α- and β-subunits. The physicochemical, immunological, and biological activities of r-hFSH are similar to those of human menopausal urine-derived hFSH, but free of urinary protein and of any luteinizing hormone (LH) component.

INDICATIONS AND CLINICAL USE

GONAL-f® is indicated for the stimulation of multiple follicular development in ovulatory patients undergoing Assisted Reproductive Technologies (ART) such as *in vitro* fertilization. To complete follicular maturation in the absence of an endogenous lutenizing hormone (LH) surge, human chorionic gonadotropin (hCG) is given.

GONAL-f® is also indicated for the stimulation of follicular development in patients with hypothalamic-pituitary dysfunction who present either oligomenorrhoea or amenorrhoea (WHO Group II). To complete follicular maturation and effect ovulation, hCG is given.

Selection of Patients

1. Before treatment with GONAL-f® is instituted, a thorough gynaecologic and endocrinologic evaluation must be performed. This should include an assessment of pelvic anatomy.
2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.
3. Appropriate evaluation should be performed to exclude 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 evaluation should always be performed in patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities before starting GONAL-f® therapy.
5. Evaluation of the partner's fertility potential should be included in the initial evaluation.

CONTRAINDICATIONS

GONAL-f® is contraindicated in women who exhibit:

1. High levels of Follicle Stimulating Hormone (FSH) indicating primary ovarian failure.
2. Uncontrolled thyroid or adrenal dysfunction.
3. An organic intracranial lesion such as a pituitary tumour or tumours of the hypothalamus.
4. The presence of any cause of infertility other than anovulation, as stated in *INDICATIONS AND CLINICAL USE* unless the women are candidates for Assisted Reproductive Technologies.
5. Abnormal uterine bleeding (see *INDICATIONS AND CLINICAL USE: Selection of Patients*).
6. Ovarian cyst or enlargement of undetermined origin (see *INDICATIONS AND CLINICAL USE: Selection of Patients*).
7. Sex hormone dependent tumours of the reproductive organs and breasts.
8. Pregnancy/lactation
9. Hypersensitivity to or history of previous allergic reaction to follitropin alfa, FSH or to any of the excipients.

WARNINGS AND PRECAUTIONS

General

Careful attention should be given to diagnosis in candidates for GONAL-f® therapy (see *INDICATIONS AND CLINICAL USE: Selection of Patients*).

GONAL-f® should only be used by physicians who are thoroughly familiar with infertility problems and their management. GONAL-f® is a potent gonadotrophic substance capable of causing mild to severe adverse reactions. Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and requires the availability of appropriate monitoring facilities (see *Monitoring and Laboratory Tests*). Safe and effective use of GONAL-f® requires monitoring of ovarian response with ultrasound, alone or in combination with measurement of serum estradiol levels, on a regular basis.

In patients with porphyria or a family history of porphyria GONAL-f® may increase the risk of an acute attack. Deterioration or a first appearance of this condition may require cessation of treatment.

Prior to therapy with GONAL-f®, 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.

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and pituitary or hypothalamus tumours, and appropriate specific treatment given.

During training of the patient for self-administration, special attention should be given to specific instructions for the use of the pen.

Overstimulation of the Ovary During FSH Therapy

Ovarian Enlargement: Use of FSH therapy to stimulate follicular development may result in the recruitment of a number of follicles. This may result in mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distention and/or abdominal pain. It is more commonly seen in women with polycystic ovarian syndrome. This degree of enlargement has been reported to occur in approximately 20% of those treated with urofollitropin and hCG, and generally regresses without treatment within two or three weeks.

To minimize the hazard associated with the occasional abnormal ovarian enlargement which may occur with GONAL-f® therapy, the lowest dose consistent with the expectation of good results should be used. Careful monitoring of ovarian response can further minimize the risk of ovarian enlargement.

If there is clinical evidence of excessive ovarian response (see *Monitoring and Laboratory Tests*), treatment should be discontinued and hCG should not be administered. This will reduce the chances of development of the Ovarian Hyperstimulation Syndrome.

Ovarian Hyperstimulation Syndrome (OHSS): OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event. It is characterized by marked ovarian enlargement, high serum sex steroids and an apparent dramatic increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities. 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 mild manifestation of OHSS: abdominal pain, abdominal distention and enlarged ovaries, severe ovarian enlargement, Moderate OHSS may additionally present nausea, vomiting, diarrhoea, ultrasound evidence of ascites and marked ovarian enlargement. Severe OHSS further includes symptoms such as severe ovarian enlargement, weight gain, dyspnea, or oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, pleural effusions, or acute pulmonary distress (see *Respiratory and Cardiovascular*). Rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events, such as pulmonary embolism, ischaemic stroke or myocardial infarction. 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 the clinical trials in oligo-anovulatory infertile women treated with GONAL-f® in which both estradiol and ultrasound measurements were utilized to monitor follicular development, the incidence of severe OHSS was 1 in 513 treatment cycles (0.2%).

In the clinical trials in ovulatory infertile women treated with GONAL-f® for induction of multiple follicular induction for IVF/ET in which both estradiol and ultrasound measurements were utilized to monitor follicular development, there was no incident of severe OHSS.

To minimize the risk of OHSS or of multiple pregnancy, ultrasound scans, as well as serum oestradiol measurements are recommended.

When risk of OHSS or multiple pregnancies is assumed, treatment discontinuation should be considered.

Independent risk factors for developing OHSS include young age, lean body mass, polycystic ovarian syndrome, higher doses of exogenous gonadotropins, high absolute or rapidly rising serum estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in ART cycles.

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 *Monitoring and Laboratory Tests*), the hCG must be withheld.

If severe OHSS occurs, treatment should be stopped and the patient should be hospitalized. A physician experienced in the management of this syndrome, or who is experienced in the management of fluid and electrolyte imbalances should be consulted.

Carcinogenesis and Mutagenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of GONAL-f®. However, r-hFSH showed no mutagenic activity in a series of tests performed to evaluate its potential genetic toxicity including, bacterial and mammalian cell mutation tests, a chromosome aberration test and a micronucleus test.

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is

not yet established whether or not treatment with gonadotropins increases the baseline risk of these tumours in infertile women.

Respiratory and Cardiovascular

The following paragraph describes serious medical events reported following gonadotropin therapy. Serious pulmonary conditions (e.g., atelectasis, acute respiratory distress syndrome and exacerbation of asthma) have been reported. In addition, thromboembolic events both in association with, and separate from 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, myocardial infarction, cerebral vascular occlusion (ischemic stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death. In women with recent or ongoing thromboembolic disease or women with generally recognized risk factors for thromboembolic events, such as personal or family history, treatment with gonadotropins may further increase the risk for aggravation or occurrence of such events.

In these women, the benefits of gonadotropin administration need to be weighed against the risks. It should be noted however, that pregnancy itself as well as OHSS also carries an increase of thromoboembolic events.

Dependence/Tolerance

There have been no reports of abuse or dependence with GONAL-f®.

Sexual Function/Reproduction

In patients undergoing ovarian stimulation, the incidence of multiple pregnancies is increased as compared with natural conception. In the event they occur, majority of multiple conceptions are twins. Reports of multiple births have been associated with GONAL-f® treatment. The risk of multiple births in patients undergoing ART procedures is related to the number of embryos replaced. In other patients, the incidence of multiple births may be increased by GONAL-f®, as has been observed with other gonadotropin preparations. The patient and her partner should be advised of the potential risk of multiple births before starting treatment. To minimize the risk of higher order multiple pregnancy, careful monitoring of ovarian response is recommended.

Since women with infertility undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities, the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
The incidence of pregnancy wastage by miscarriage or abortion may be higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than following natural conception in the normal population.

The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conception. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and multiple pregnancies.

Impaired fertility has been reported in rats exposed to pharmacological doses of r-hFSH (40 IU/kg/day) for extended periods through reduced fecundity.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Given in high doses (>5 IU/kg/day), GONAL-f® caused an increase in deaths, fetal effects and dystocia in pregnant rats and rabbits, but without being a teratogen. However, since GONAL-f® is not indicated in pregnancy, these data are of limited clinical relevance. To date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Nursing Mothers: It is not known whether this drug is excreted in human milk, although animal studies have shown that r-hFSH is excreted in milk. Therefore, GONAL-f® is contraindicated in lactating mothers. During lactation, the secretion of prolactin can entail a poor prognosis to ovarian stimulation.

Pediatrics: Not indicated for treatment in pediatric population.

Geriatrics: Not indicated for treatment in the geriatric population.

Renal or hepatic impaired patients

Safety, efficacy, and pharmacokinetics in patients with renal or hepatic impairment have not been established.

Monitoring and Laboratory Tests

In most instances, treatment with GONAL-f® results only in follicular recruitment and development. In the absence of an endogenous LH surge, hCG is given when monitoring of the patient indicates that sufficient follicular development has occurred. This may be estimated by ultrasound alone or in combination with measurement of serum estradiol levels. The combination of both ultrasound and serum estradiol measurement are useful for monitoring the development of follicles, for timing of the ovulatory trigger, 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 estrogens do 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 most generally used are as follows:

1. A rise in basal body temperature,
2. Increase in serum progesterone, and
3. Menstruation following a shift in basal body temperature.

When used in conjunction with the 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 follicle development and maturation require a physician who is experienced in the interpretation of these tests.

For patients undergoing extended cycles of treatment, PTT and liver enzymes should be monitored.

Occupational Hazards
No studies on the effects on the ability to drive and use machines have been performed.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Safety data on GONAL-f® stem from clinical studies, as well as 15 years of post-marketing surveillance.

The most commonly reported adverse reactions with GONAL-f® in clinical studies were ovarian cysts, injection site reaction of any severity, headache, mild to moderate ovarian hyperstimulation syndrome (OHSS) manifesting with symptoms such as abdominal swelling and pain, ovarian enlargement, as well as gastrointestinal symptoms such as nausea, vomiting, and diarrhoea.

The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of GONAL-f®, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) was severe OHSS and its associated complications, such as ovarian torsion, thromboembolic events, and pulmonary conditions (see *WARNINGS AND PRECAUTIONS*).

Severe OHSS was also the most frequently reported serious adverse reaction. (see *WARNINGS AND PRECAUTIONS*). Complications of severe OHSS have been reported both in clinical studies and from spontaneous sources.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Summary of Adverse Drug Reactions Reported during Clinical Trials and in Post-Market Experience

More than 1000 patients were exposed to r-hFSH during the clinical development programme of GONAL-f®. In addition to the clinical trial patient population, it is estimated that 580 000 to 1 700 000 patients have been exposed to r-hFSH during the post-marketing phase. The following summary presents the adverse drug reactions that have been reported with the use of r-hFSH during clinical trials and during post-market use. These data provide a comprehensive description of the safety profile of GONAL-f®.

≥ 1% (Common and Very Common)

Reproductive disorders, female

- Ovarian cysts
- Mild to moderate ovarian enlargement
- Breast tenderness
- Mild to moderate OHSS

Application site disorders:

- Mild to severe injection site reaction (e.g. pain, redness, bruising, swelling and/or irritation at the site of injection)

Body as a whole, general disorders:

- Headache

Gastro-intestinal system disorders:

- Abdominal; pain, distension, cramps, discomfort
- Nausea
- Vomiting
- Diarrhea

< 1% (Uncommon, Rare and Very rare)

Reproductive disorders, female:

- Severe OHSS
- Complications of severe OHSS (see warnings and precautions sections)

Vascular (extracardiac) disorders:

- Thromboembolism

Respiratory system disorders:

- Acute pulmonary distress
- Exacerbation or aggravation of asthma

Immune system disorders;

- Mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Common and very common ADR have been reported from clinical studies, as well as in post-marketing surveillance. Severe OHSS has been reported from clinical studies, as well as in post-marketing surveillance. However, rare and very rare ADRs such as complications of severe OHSS and allergic reactions have generally been reported from post-marketing sources.

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

1. Pulmonary and vascular complications (see *WARNINGS AND PRECAUTIONS*)
2. Ovarian Hyperstimulation Syndrome (see *WARNINGS AND PRECAUTIONS*)
3. Adnexal torsion (as a complication of ovarian enlargement)
5. Mild to moderate ovarian enlargement
6. Abdominal pain
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 (body rash, hives/urticaria)

Subjective assessments indicated minimal or mild transient pain in two and five subjects who received GONAL-f® single-dose and GONAL-f® multi-dose, respectively.

The following medical events have been reported subsequent to pregnancies resulting from GONAL-f® therapy in controlled clinical trials:

1. Spontaneous Abortion
2. Ectopic Pregnancy
3. Premature Labour
4. Postpartum Fever
5. Congenital abnormalities

Two incidents of congenital cardiac malformations have been reported in children born following pregnancies resulting from treatment with GONAL-f® and hCG in clinical studies. In addition, a pregnancy occurring in a study following treatment with GONAL-f® and hCG was characterized by apparent failure of intrauterine growth and terminated for a suspected syndrome of congenital abnormalities. No specific diagnosis was made.

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.

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.

DRUG INTERACTIONS

Clomiphene citrate, LH and hCG used with GONAL-f® may enhance follicular response, and caution is indicated when using these drugs together.

Use of GnRH agonist or antagonist to induce pituitary desensitization may alter the dosage of GONAL-f® needed.

No other clinically significant drug/drug or drug/food interactions have been reported during GONAL-f ® therapy.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Treatment with GONAL-f® Pen should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

GONAL-f® Pen is intended for subcutaneous administration.

Recommended Dose and Dosage Adjustment

The dose of GONAL-f® to stimulate development of the follicle must be individualized for each patient and the particular indication. To minimize the hazard associated with the occasional abnormal ovarian enlargement which may occur with GONAL-f® therapy, the lowest dose consistent with the expectation of good results should be used. GONAL-f® should be administered subcutaneously until adequate follicular development is indicated by ultrasound alone or in combination with measurement of serum estradiol levels.

The dosage recommendations given for GONAL-f® are those in use for urinary FSH. Clinical assessment of GONAL-f® indicates that its daily doses, regimens of administration, and treatment monitoring procedures should not be different from those currently used for urinary FSH-containing preparations. However, when these doses were used in a clinical study comparing GONAL-f® and urinary FSH, GONAL-f® was more effective than urinary FSH in terms of a lower total dose and a shorter treatment period needed to achieve pre-ovulatory conditions.

Over the course of treatment, doses may range between 75 to 450 IU depending on the indication and the individual patient response. To complete follicular development and effect ovulation in

the absence of an endogenous LH surge, hCG is given when monitoring of the patient indicates that sufficient follicular development has occurred. If the ovaries are abnormally enlarged or significant abdominal pain occurs, GONAL-f® treatment should be discontinued, hCG should not be administered, and the patient should be advised to refrain from intercourse until resolution of the cycle; this will reduce the chances of development of the Ovarian Hyperstimulation Syndrome and, should spontaneous ovulation occur, reduce the chances of multiple gestation. While individual dosing regimens will differ between patients, typical treatment regimens are presented below.

Assisted Reproductive Technologies

In patients undergoing Assisted Reproductive Technologies (ART) whose endogenous gonadotropin levels are not suppressed, GONAL-f® should be initiated in the early follicular phase (cycle day 2 or 3) at a dose of 150 IU per day, administered subcutaneously. Treatment should be continued until adequate follicular development is indicated as determined by either ultrasound alone or in combination with measurement of serum estradiol levels. Adjustments to dose, based on the patient's response, should only be considered after the first five days of treatment; subsequently dosage should be adjusted no more frequently than every 3-5 days and by no more than 37.5-150 IU additionally at each adjustment. Treatment should be continued until adequate follicular development is indicated. Once adequate follicular development is evident, hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval.

In patients undergoing ART, whose endogenous gonadotropin levels are suppressed indicating a hypogonadotrophic state, GONAL-f® should be initiated at a dose of 225 IU per day, administered subcutaneously. Treatment should be continued until adequate follicular development is indicated as determined by either ultrasound alone or in combination with measurement of serum estradiol levels. Adjustments to dose may be considered after five days based on the patient's response; subsequently dosage should be adjusted no more frequently than every 3-5 days and by no more than 37.5-150 IU additionally at each adjustment. Doses greater than 450 IU per day are not generally recommended. As before, once adequate follicular development is evident hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval.

Ovulation Induction

The majority of patients who require ovulation induction are patients with Polycystic Ovarian Syndrome (PCO). Patients with PCO tend to show a more rapid and exaggerated response to treatment. Therefore, in this patient population, particular care should be employed to ensure that patients are adequately monitored and that the lowest dose consistent with the expectation of good results is employed.

It is recommended that treatment of any patient be initiated at a dose of 75 IU GONAL-f® per day, administered subcutaneously. An incremental adjustment in dose of up to 37.5 IU may be considered after 14 days. Further dose increases of the same magnitude could be made, if necessary, every seven days. Treatment duration should not exceed 35 days unless an estradiol rise indicates imminent follicular development. Once adequate follicular development is evident, hCG should be administered to induce final follicular maturation and effect ovulation.

The patient should attempt to have intercourse at a consistent frequency of at least three times/week from the day prior to administration of hCG until ovulation becomes apparent.

If there is evidence of ovulation but pregnancy does not ensue, this regimen should be repeated for at least two more courses before increasing the dose of GONAL-f® to 150 IU per day for 7 to 12 days. As before, this dose should be followed by the administration of hCG when adequate follicular development is evident. 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.

Missed Dose

For patients who miss a dose, it is not recommended to double the next dose. The patients should be reminded to contact the physician monitoring their treatment.

Administration

Each GONAL-f® Pen is designed to administer multiple doses liquid solution of GONAL-f® subcutaneously.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Aside from possible ovarian hyperstimulation and multiple gestations (see *WARNINGS AND PRECAUTIONS*), little is known concerning the consequences of acute overdosage with GONAL-f®. Apart from expected ovarian and endometrial effects, no acute toxicity was seen in animals given doses of r-hFSH up to 1000-fold the human dose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Follicle stimulating hormone (FSH, follitropin) is one of the key hormones regulating reproductive functions both in females and in males. In females, it stimulates the development of ovarian follicles that carry the oocytes, while in males it promotes spermatogenesis.

FSH is synthesized by gonadotrophic cells of the anterior pituitary gland and secreted into the general circulation through which it reaches specific target cells in the ovaries and testes. The synthesis and the secretion of FSH are stimulated by a hypothalamic peptide named gonadotropin-releasing hormone (GnRH). In the target organ, FSH binds to the FSH receptor, a protein component of ovarian granulosa cells and testicular Sertoli cell plasma membranes. FSH binding to its receptor triggers intracellular mechanisms that regulate steroidogenesis, cell replication, and expression of specific proteins and growth factors that modulate gametogenesis.

GONAL-f® stimulates ovarian follicular growth in women who do not have primary ovarian failure. FSH is the primary hormone responsible for follicular recruitment and development. To complete follicular maturation and effect ovulation in the absence of an endogenous LH surge, hCG is given 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, with lack of response to FSH in some patients.

Pharmacodynamics

One main PD study has been performed in healthy female volunteers down-regulated with a GnRH agonist (Study 5117). The aim of this study was to assess PD characteristics of r-hFSH administered sc daily for one week. After s.c. administration over one week, the first PD marker of ovarian response to FSH was serum inhibin, followed by plasma E2 and follicular growth. When FSH administration was stopped, inhibin levels dropped, while E2 continued to rise for one day and follicle size further increased during four days.

Two thirds of the volunteers developed significant follicular growth followed by corresponding decreasing levels of inhibin and increasing levels of E2 secretion. Moreover, no correlation was found between maximal serum FSH concentrations during administration and the maximal E2 responses, inhibin responses and follicular growth responses

Pharmacokinetics

Single dose pharmacokinetics of r-hFSH were determined following intravenous, administration of 150 IU and 300 IU of GONAL-f® to 12 healthy, down-regulated female volunteers (Study 5007). Single pharmacokinetics of r-hFSH were determined following intravenous, subcutaneous and intramuscular administration of 150 IU GONAL-f® to 12 healthy, down-regulated female volunteers. Steady-state pharmacokinetics were also determined in the same 12 healthy down-regulated female volunteers who were administered a single daily dose of 150 IU for seven days (Study 5117). The pharmacokinetic parameters from these studies are included in the tables below.

Table 1: Summary of r-hFSH pharmacokinetic parameters in healthy female volunteers (Study 5007)

	C_{max} (IU/L)	$t_{½}$ (h)	$AUC_{0-\infty}$ IU-hr/L	Clearance (L/h)	Volume of distribution V_{ss} (L)
Single dose IV (150 IU)	32 ± 10	14 ± 7	274 ± 71	0.6 ± 0.2	10 ± 6
Single dose IV (300 IU)	59 ± 18	17 ± 3	598 ± 126	0.6 ± 0.1	11 ± 6

Table 2: Summary of r-hFSH pharmacokinetic parameters in healthy female volunteers (Study 5117)

	C_{max} (IU/L)	$t_{½}$ (h)	AUC IU-hr/L	Clearance (L/h)	Volume of distribution V_{ss} (L)
Single dose IV (150 IU)	33 ± 9	15 ± 5	286 ± 78	0.6 ± 0.2	9 ± 3
Single dose IM (150 IU)	3 ± 1	50 ± 27	206 ± 66	---	---
Single dose SC (150 IU)	3 ± 1	24 ± 11	176 ± 87	---	---
Multiple dose SC (7x150 IU)	4 ± 1[(1)] 9 ± 3[(2)]	24 ± 8	187 ± 61[#]	---	---

[#] Steady-state $AUC_{144-168}$ (After the 7th daily SC dose)

(1) After the frst dose
(2) After the last dose

Following intravenous administration, GONAL-f® is distributed to the extracellular fluid space with an initial half-life of approximately 2 hours and eliminated from the body with a terminal half-life of approximately 1 day. The steady-state volume of distribution and total clearance are 10 L and 0.6 L/h, respectively. One-eighth of the GONAL-f® dose is excreted in the urine.

Following subcutaneous or intramuscular administration, the absolute bioavailability is 70%. Following repeated administration, GONAL-f® accumulates 3-fold at steady-state within 3-4 days. In women whose endogenous gonadotrophin secretion is suppressed, GONAL-f® has been shown to effectively stimulate follicular development and steroidogenesis, despite unmeasurable LH levels.

Special Populations and Conditions
No studies have been conducted with special populations and conditions.

STORAGE AND STABILITY

Pharmacy: Store at 2 - 8 °C (in a refrigerator) for up to 2 years.

Patient: Store at 2 - 8 °C (in a refrigerator) **or** store for a single period between 2 and 25 °C (in the refrigerator or at room temperature) for a maximum of 3 months. After first use, the pen may be stored 25 °C (room temperature) for a maximum of 28 days.

Do not use the GONAL-f® prefilled pen if the solution contains particles or is not clear.

Do not freeze. Protect from light.

Keep in a safe place out of the reach of children.

Do not use after the expiry date.

SPECIAL HANDLING INSTRUCTIONS

The GONAL-f® solution should not be administered if it contains particles or is not clear.

GONAL-f® Pen is not designed to allow the cartridge to be removed or any other drug to be mixed in the cartridge.

Discard used needles immediately after injection.

Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

GONAL-f® Pen is presented as solution for injection in 3 mL cartridge (Type I glass), with a plunger stopper (halobutyl rubber) and a rubber crimp cap (halobutyl rubber). The cartridge is preassembled with the prefilled pen. GONAL-f® Pen is shatterproof per EN ISO 11608-1:2000 standards.

GONAL-f® Pen is available in the following strengths and packages are available:

- 300 IU/0.48 mL (21.84 mcg/0.48 mL Filled by Mass: 1 prefilled pen and 8 needles to be used with the pen for subcutaneous administration,
- 450 IU/0.72 mL (32.76 mcg/0.72 mL) Filled by Mass: 1 prefilled pen and 12 needles to be used with the pen for subcutaneous administration,
- 900 IU/1.44 mL (65.51 mcg/1.44 mL) Filled by Mass: 1 prefilled pen and 20 needles to be used with the pen for subcutaneous administration.

Each pen also contains the following non-medicinal ingredients: disodium phosphate dihydrate, L-methionine, m-cresol, phosphoric acid, poloxamer 188, sodium dihydrogen phosphate monohydrate, sodium hydroxide, sucrose and water for injection

There is no latex in the components of the prefilled pen.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Follitropin alfa (approved INN)

Chemical name: recombinant human Follicle Stimulating Hormone for Injection (r hFSH)

Molecular Weight: α-subunit: 14 Kda β-subunit: 17 Kda

Molecular Formula: $C_{975}H_{1515}N_{267}O_{305}S_{26}$

Structural Formula: Amino acid sequence of follitropin alfa:

Alpha subunit:																			
Ala	Pro	Asp	Val	Gln	Asp	Cys	Pro	Glu	Cys	Thr	Leu	Gln	Glu	Asn	Pro	Phe	Phe	Ser	**19**
Gln	Pro	Gly	Ala	Pro	Ile	Leu	Gln	Cys	Met	Gly	Cys	Cys	Phe	Ser	Arg	Ala	Tyr	Pro	**38**
Thr	Pro	Leu	Arg	Ser	Lys	Lys	Thr	Met	Leu	Val	Gln	Lys	Asn	Val	Thr	Ser	Glu	Ser	**57**
Thr	Cys	Cys	Val	Ala	Lys	Ser	Tyr	Asn	Arg	Val	Thr	Val	Met	Gly	Gly	Phe	Lys	Val	**76**
Glu	Asn	His	Thr	Ala	Cys	His	Cys	Ser	Thr	Cys	Tyr	Tyr	His	Lys	Ser	**92**			
Beta subunit:																			
Asn	Ser	Cys	Glu	Leu	Thr	Asn	Ile	Thr	Ile	Ala	Ile	Glu	Lys	Glu	Glu	Cys	Arg	Phe	**19**
Cys	Ile	Ser	Ile	Asn	Thr	Thr	Trp	Cys	Ala	Gly	Tyr	Cys	Tyr	Thr	Arg	Asp	Leu	Val	**38**
Tyr	Lys	Asp	Pro	Ala	Arg	Pro	Lys	Ile	Gln	Lys	Thr	Cys	Thr	Phe	Lys	Glu	Leu	Val	**57**
Tyr	Glu	Thr	Val	Arg	Val	Pro	Gly	Cys	Ala	His	His	Ala	Asp	Ser	Leu	Tyr	Thr	Tyr	**76**
Pro	Val	Ala	Thr	Gln	Cys	His	Cys	Gly	Lys	Cys	Asp	Ser	Asp	Ser	Thr	Asp	Cys	Thr	**95**
Val	Arg	Gly	Leu	Gly	Pro	Ser	Tyr	Cys	Ser	Phe	Gly	Glu	Met	Lys	Glu	**111**			

Asn: N-glycosylation sites

Relevant Physicochemical Properties:

r-hFSH consists of two non-covalently linked, non-identical protein components designated as the α- and β-subunits. The α-subunit is composed of 92 amino acids carrying two carbohydrate moieties linked to Asn-52 and Asn-78. The β-subunit is composed of 111 amino acids carrying two carbohydrate moieties linked to Asn-7 and Asn-24. r-hFSH is derived from a Chinese Hamster Ovary cell line which has been modified by the addition of the human genes encoding the FSH α- and β-chains.

pH: 6-8

CLINICAL TRIALS

Controlled ovarian hyperstimulation in assisted reproductive technologies

In vitro Fertilization

Two-phase III studies were performed to compare the clinical efficacy and safety of GONAL-f® (follitropin alfa for injection) 75 IU with that of Metrodin HP 75 IU (uhFSH-HP). The two studies had a similar prospective randomized design.

Study demographics and trial design

Table 3: Summary of patient demographics for clinical trials in ART

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number randomized)	Mean age (SD)	Gender
Bergh (Study 8237)	Prospective, assessor-blind, randomized, parallel-group, multicentre study.	150 IU/day for the first 6 days. Dose adjustments on Day 7 and 9 based on ovarian response	235	32.0 ± 3.5 (r-hFSH) 31.2 ± 5.3 (Metrodin HP)	Female
Frydman (Study 8407)	Prospective, double blind, randomized, parallel group, multicentre study.	150 IU/day for the first 6 days. Dose adjustments on Day 7 and 9 based on ovarian response	278	31.4 ± 3.5 (r-hFSH) 31.2 ± 4.0 (Metrodin HP)	Female

Patients enrolled in both trials were between 18 and 38 years old with a mean age around 32, with regular menstrual cycles of 25–35 days; no ecographic signs of PCO disease, have an infertility due to any of the following factors: tubal factor, mild endometriosis, male factor or unexplained factor; no more than three previous assisted reproduction attempts; presence of both ovaries and a normal uterine cavity; a BMI up to 28 kg/m^2, no history of either OHSS or poor response to gonadotropin therapy, no azoospermia or clinical signs of infection detected in a semen analysis within the previous 12 months.

Study results

Table 4: Results of study 8237 (Bergh) in Controlled ovarian hyperstimulation prior to ART

Primary Endpoint	GONAL-f® 75 IU	Metrodin HP 75 IU	p-value
Oocytes retrieved (mean ± SD)	12.2 ± 5.5	7.6 ± 4.4	<0.001

Two hundred and thirty seven patients were recruited in the study and received the down regulation, 119 of them were randomized in the GONAL-f® group and 118 in the

Metrodin HP group. These patients were included in the analysis of demography and in the analysis of safety.

Two hundred and thirty-five patients received stimulation, 119 of them were in the GONAL-f® group and 116 in the Metrodin HP group.

Two hundred and twenty-one patients received hCG and so were included in the analysis of efficacy. One hundred and nineteen (100 %) of them were in the GONAL-f® treatment group and 102 (87 %) were in the Metrodin HP treatment group.

The mean number of oocytes recovered (primary endpoint) was higher in the r-hFSH compared to the u-hFSH- HP group (12.2 vs. 7.6 respectively; $p < 0.001$). On the other hand, the number of FSH treatment days (11.0 vs. 13.5) and the number of 75 IU ampoules (21.9 vs. 31.9) used were significantly less ($p < 0.001$) in the r-hFSH group than in the u-hFSH-HP group. The mean numbers of embryos obtained were 8.1 vs. 4.7 ($p < 0.001$) in favor of the r-hFSH group.

The clinical pregnancy rates per started cycle and per embryo transfer were 45 and 35%, and 48 and 46%, respectively in the r-hFSH and u-hFSH-HP groups (not significant).

Table 5: Results on stimulation and gamete characteristics (Study 8237)

Parameter	**GONAL-f®**	**u-hFSH HP**	**p value**
N patients randomized	119	116	
N of patients receiving hCG	119	102	
N of days FSH treatment	11.0 ± 1.6	13.5 ± 3.7	<0.001
N of ampoules FSH (75 IU equiv.)	21.9 ± 5.1	31.9 ± 13.4	<0.001
Follicles >10 mm day of hCG	12.7 ± 4.9	8.4 ± 4.2	0.002
E2 (nmol/l) day of hCG	6.55 ± 5.75	3.95 ± 3.90	<0.001
Oocytes retrieved	12.2 ± 5.5	7.6 ± 4.4	<0.001
N Oocyte nuclear maturity N (%)	634 (83)	323 (79)	ns
N of cleaved embryos on day 2	8.1 ± 4.2	4.7 ± 3.5	<0.001
N of embryos cryopreserved	3.2 ± 3.0	1.7 ± 2.5	<0.001
N of Patients with embryo transfer (%)	111/119 (93.3)	89/116 (76.7)	

Table 6: Results of study 8407 (Frydman) in Controlled ovarian hyperstimulation prior to ART

Primary Endpoint	**GONAL-f® 75 IU**	Metrodin HP **75 IU**	**p-value**
Oocytes retrieved (mean ± SD)	11.0 ± 5.9	8.8 ± 4.8	0.044

Two hundred and seventy-eight (278) patients were enrolled in this study: 139 were randomized in the GONAL-f® group and 139 in the Metrodin HP group. The efficacy analysis of this study was performed on all randomized patients who received hCG (246): 130 in the GONAL-f® group and 116 in the Metrodin HP group, apart from the pregnancy criteria which were analysed successively in the Starting FSH Patient population, the population of patients where oocyte recovery was carried out and the population of patients having had embryo transfer.

The mean number of oocytes (primary endpoint) retrieved was higher in the r-hFSH group (11.0 ± 5.9 vs. 8.8 ± 4.8; p = 0.044). There were also significant differences between the two groups in several of the secondary efficacy parameters, mainly fewer days of FSH stimulation were required with r-hFSH to reach the criteria for triggering follicle maturation than with u-hFSH HP (11.7 ± 1.9 versus 14.5 ± 3.3 respectively; p < 0.001). Correspondingly, the total dose of FSH required to reach these criteria was lower for r-hFSH than u-hFSH HP (27.6 ± 10.2 x 75 IU ampoules, compared with 40.7 ± 13.6; p < 0. 001). Only 56.2% of patients in the r-hFSH group required an increase in dosage after the first 6 days of treatment, compared with 85.3% of those receiving u-hFSH HP (p = 0.001).

The initial pregnancy rate (excluding biochemical) per started cycle was 32/139 (23.0%) for r-hFSH and 38/139 (27.3%) for u-hFSH HP (not significant).

Table 7: Results on stimulation and gamete characteristics (Study 8407)

Parameter	Gonal-F®	u-hFSH HP	p value
No. of patients starting FSH	139	139	
No. of patients receiving hCG	130	116	
No. of days FSH treatment	11.7 ± 1.9	14.5 ± 3.3	<0.001
No. of ampoules FSH (75 IU equiv.)	27.6 ± 10.2	40.7 ± 13.6	<0.001
Follicles > 12 mm day of hCG	12.1 ± 5.2	10.5 ± 4.6	0.004
Oocytes retrieved	11.0 ± 5.9	8.8 ± 4.8	0.044
Oocyte nuclear maturity B MII No.	8.1 ± 4.4	6.3 ± 3.5	0.001
No. of embryos obtained	5.0 ± 3.7	3.5 ± 2.9	< 0.001
No. of patients with embryo transfers/hCG received	116 (89%)	98 (84%)	
No. of embryos transferred/cryopreserved	3.5 ± 2.8	2.6 ± 2.2	0.009
No. ongoing clinical pregnancies/cycle started	25 (18%)	25 (18%)	NS
% multiple pregnancies	9	7	NS

Both studies confirm that r-hFSH is more effective than u-hFSH HP in inducing ovulation in women undergoing assisted reproductive treatment. Patients given the recombinant product required fewer days of treatment and a lower total dose of FSH to reach the criteria for hCG administration than those receiving u-hFSH HP.

Ovulation induction

Study demographics and trial design

Table 8: Summary of patient demographics for clinical trials in OI

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number randomized)	Mean age (SD)	Gender
Study 5642	Phase III, open label, randomized, comparative, parallel group, multicenter	75 IU as starting dose on day 3-5. Dose adjustments every 7 days by dose of 37.5 IU every 7 days not before than day 14	222	29.3 +/- 3.2 (r-hFSH) 29.1+ 3.6 (Metrodin HP)	female
Study 5727	Phase III, open label, randomized, comparative, parallel group, multicenter	75 IU as starting dose on day 3-5. Dose adjustments every 7 days by dose of 37.5 IU every 7 days not before than day 14	232	29.3 +/- 3.7 (r-hFSH) 30.0 + 3.4 (Metrodin HP)	female

Both studies recruited the same population: women between 18 and 39 years old; ovulatory dysfunction: either anovulation or oligoovulation who had failed to ovulate or conceive when treated for at least 3 months with clomiphene citrate; BMI less than 35.

Study results

Table 9: Results of study 5642 in OI

Primary Endpoints	Associated value and statistical significance for GONAL-f® at specific dosages	Associated value for Metrodin (u-HP)
Cumulative ovulation rate	88% (P=0.071)	95%

The primary efficacy parameter was the ovulation rate. Two hundred and twenty-two patients entered into the first cycle of treatment, of whom 110 received GONAL-f® and 112 received Metrodin HP. In study GF 5642, the cumulative ovulation rate was 84% and 91% in the GONAL-f® and Metrodin HP treatment groups respectively. This difference was not statistically significant. The 95% confidence interval of the difference in the cumulative ovulation rate between the Metrodin HP and GONAL-f® treatment groups was [-1.3%; 16.17%] which is less than the 20% difference defined as the limit of the clinically acceptable difference between the two treatment groups. Seventy-five patients delivered at least one baby during this study, 31 (28%) in the GONAL-f® treatment group and 44 (39%) in the Metrodin HP treatment group. No statistically significant difference was recorded between the two treatment groups. The overall

multiple pregnancy rate was 6% and 14% in the GONAL-f® and Metrodin HP treatment group, respectively.

Table 10: Results of study 5727 in OI

Primary Endpoints	Associated value and statistical significance for GONAL-f® at specific dosages	Associated value and statistical significance for Metrodin (u-HP)
Cumulative ovulation rate	88% (ns)	95% (ns)

The second study showed similar results in terms of efficacy endpoint. The patient ovulation rate in patients with known ovulation outcome was 88% in the GONAL-f® treatment group and 95% in the Metrodin HP treatment group. This difference is not statistically significant. The one-sided confidence interval for the difference in ovulation rates in the GONAL-f® and Metrodin HP treatment groups was (-12.8%, ∞), confirming that the ovulation rate for patients treated with GONAL-f® is as good as and equivalent to the ovulation rate of those treated with Metrodin HP because the absolute value of the difference in ovulation rates is less than the specified 20%.

Sixty-six patients delivered at least one baby during this study, 34 (29%) in the GONAL-f® treatment group and 32 (28%) in the Metrodin HP treatment group. No statistically significant difference was recorded between the two treatment groups. The overall multiple pregnancy rate was 5% and 4% in the GONAL-f® and Metrodin HP treatment group, respectively.

Comparative Bioavailability Studies

Study IMP23572

Study Demographics and Design

Table 11: Summary of patient demographics for clinical study 23572

Study	Trial design	Dosage, route of administration and duration	Study subjects (n=number randomized)	Mean age (SD)	Gender
Study 23572	Phase I, open-label, cross-over.	2 single injections of 300 IU r-hFSH (either f.d. or liquid) s.c. at 7 days interval	39	18-45 years	Female & Male

Study Results

The bioequivalence of the new liquid formulation has been assessed versus a freeze dried formulation. Mean values of C_{max} and AUC_{last} were very similar for both formulation and mean values of T_{max} were also similar- The 90 % confidence intervals of the ratios of AUC_{last} and C_{max} were within the pre-defined range of 0.8 to 1.25.

Table 12: Summary Table of Comparative Bioavailability Parameters

r-hFSH (Multidose vs Monodose Freeze-dried) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**r-hFSH Multidose Liquid (Test)**	**r-hFSH Monodose Freeze-dried (Reference)**	**% Ratio of Geometric Means (following correction for potency)**	**90% Confidence Interval (following correction for potency)**
AUC_T (IU·h/L)	487.8 499.9 (22.3)	544.6 552.8 (18.6)	104%	99% – 111%
AUC_I (IU·h/L)	544.6 564.1 (25.8)	614.0 634.0 (24.4)	Not evaluated	Not evaluated
C_{MAX} (IU/L)	6.7 6.9 (25.3)	7.5 7.7 (24.0)	105%	100% - 109%
T_{MAX} (h)	15 (6 – 48)	12 (4 – 48)		
$T_{½}$ (h)	36.1 (56.8)	37.5 (60.9)		

The tolerability of multi-dose liquid GONAL-f® was compared to a reference GONAL-f® mono-dose freeze-dried formulation in pituitary gonadotrope down-regulated male and pre-menopausal female volunteers. The liquid formulation was well tolerated, and no serious or severe adverse events were reported. Eleven (11) adverse events were reported with the liquid multi-dose formulation (11/41 = 26.8%) versus 15 with the freeze-dried formulation (15/40 = 32.5 %). The most frequently reported adverse event was headache for both formulations.

DETAILED PHARMACOLOGY

Animal

Pharmacodynamics

To confirm that r-hFSH possessed the well-characterized pharmacodynamic activity of human FSH, both *in vivo* and *in vitro* studies were conducted. The *in vivo* studies, involving rats and monkeys, compared r-hFSH with two u-hFSH products (Metrodin7 and Fertinorm7 HP). The *in vitro* studies compared r-hFSH with international human pituitary FSH reference standards as well as with the two u-hFSH products.

In vitro

In an *in vitro* study using calf testes membrane, r-hFSH had the same binding characteristics to the testicular FSH receptor as did reference standards of human pituitary FSH (US NIADDK preparation h-FSH-1-3 and WHO 1st International Standard 83/575) and the two u-hFSH preparations. The binding affinities were very similar for all of the products, and the binding curves were superimposable.

The bioactivity of r-hFSH was indistinguishable from that of the two u-hFSH preparations and from pituitary and urinary FSH reference standards in a bioassay that measures FSH bioactivity according to estradiol production in isolated ovarian granulosa cells.

In vivo

Pharmacological studies *in vivo* included a comparison of the quantitative dose-response curves of r-hFSH and two clinical preparations of u-hFSH for oocyte formation, and ovarian weight gain (also in comparison with hMG) in young female rats using the Steelman-Pohley ovarian weight gain assay. The activities of the preparations were identical. r-hFSH also produced follicular maturation in mature cynomolgus monkeys similar to that produced with u-FSH.

Pharmacokinetics

In the rat single and repeated dose ADME studies were performed with ^{125}I-labelled r-hFSH administered subcutaneously (SC) and intravenously (IV). The bioavailability of the SC dose appeared similar to that after IV administration, but elimination was slower. Radioactivity distributed in high concentrations to the thyroid gland, gastrointestinal tract, kidneys and ovaries. Radioactivity distributed to the fetus as to a non-target tissue, with concentrations less than those in maternal plasma, and radioactivity was also found in the milk of lactating female rats. Intact ^{125}I-r-hFSH was present in plasma for up to 24 hours after dosing but only a series of smaller radioactive products, probably peptide fragments, were found in the urine. The kidneys appeared to be the primary route of excretion. There were no important differences between males and females as well as between non-gravid and gravid females.

In a single dose study in monkeys, r-hFSH was shown to behave similarly to native human urinary FSH (u-hFSH) after IV administration. Both preparations followed a two-compartment model with nearly identical distribution and terminal half-lives (approximately 1.5 and 15 hours, respectively). Their volumes of distribution and total clearance were only slightly different and biologically insignificant. The pharmacokinetic parameters of r-hFSH were also similar when

administered as a single dose by the intramuscular (IM) and subcutaneous (SC) routes, and their absolute bioavailability was about 75%.

After repeated IM and SC administration of r-hFSH to monkeys, the pharmacokinetics was similar to that observed after a single dose. Steady state was reached after 2 to 3 days of treatment with an accumulation factor of about two between the first and last dose by both routes of administration.

Monitoring of serum FSH concentrations in the multidose toxicity studies demonstrated extensive exposure in monkeys and dogs, indicating that the studies were a valid test of the effects of r-hFSH. The similar bioavailabilities of r-hFSH observed in the monkey and humans would also indicate that animal results can be extrapolated to humans.

Human

Pharmacodynamics

An evaluation of the dynamics of r-hFSH was performed in 12 pituitary down-regulated healthy female volunteers. The study was divided into two parts. In part I, r-hFSH was administered in a balanced, random order, cross-over sequence as a single-dose of 150 IU on three occasions: IV, IM, and SC, each separated by a one week washout period. In Part II, each subject received a daily SC dose of 150 IU r-hFSH over seven days. The pharmacodynamics of r-hFSH were assessed by measuring daily plasma estradiol concentrations, serum immunoreactive inhibin and follicular growth by ultrasound of the ovaries - before, during, and after the seven days of treatment in Part II of the study. In this study, it was not intended to induce full follicular development and ovulation, but rather to document individual ovarian response to this predetermined fixed dose and duration of FSH treatment.

Mean serum FSH levels reached a steady state after 3-5 days. The first pharmacodynamic marker of ovarian response to FSH was serum inhibin, followed by plasma estradiol, then follicular growth (measured by total volume of follicles > 10 mm diameter). When FSH administration was stopped, inhibin levels dropped while estradiol continued to rise for one day. Follicle size continued to increase over the next four days. When individual responses were analyzed, it was noted the two thirds of the volunteers developed significant follicular growth, inhibin and estradiol secretion. No correlation was found between maximal concentration of r-hFSH and the maximal effects observed. This data indicates that the interindividual variability observed in the ovarian response to FSH therapy is not related to the pharmacokinetics of FSH, but reflects different levels of ovarian sensitivity to FSH.

Pharmacokinetics

In addition to the kinetic evaluation performed in Part I of the study summarized above under *Pharmacodynamics*, one other kinetic study was performed. This study also used 12 pituitary down-regulated, healthy female volunteers, and was a randomized, cross-over study to compare the pharmacokinetics of 150 IU Metrodin (urofollitropin for injection), 150 IU Fertinorm HP (highly purified Follicle Stimulating Hormone) and 150 IU and 300 IU of r-hFSH given intravenously.

The mean serum FSH concentration-time profiles after a single 150 dose IV of Metrodin, Fertinorm HP, and r-hFSH were superimposable, and the mean profile after a single 300 IU dose

of r-hFSH was double that of the 150 IU dose. Total clearance of the preparations was comparable. Based on the immunoassay results, the clearance of u-hFSH was 0.1 L/h while for r-hFSH it was 0.07 L/h, indicating that less than one-fifth of the administered dose was excreted in the urine. Immunoassay data showed that the FSH preparations had similar initial (2 hours) and terminal (17 hours) half-lives. The volumes of distribution at steady state (11 L) were also similar.

Comparison of various routes of administration for r-hFSH demonstrated that two thirds of the administered dose was available systemically after IM or SC injection, and the absolute bioavailability was about 70% when assessed by immunoassay. The accumulation factor for repeated SC administration was around three when steady state was reached.

TOXICOLOGY

Acute Toxicity

The single dose toxicity studies performed with r-hFSH have been summarized below in Table 13.

Table 13: Acute Toxicity Studies

Species (Strain)	#/Sex/Group	Route	Dose (IU/kg)	$LD_{50\ (IU/kg)}$
Rat (Sprague Dawley)	15	SC	1000, 2000, 4000	> 4000
	15	IM	1000, 2000, 4000	> 4000
	20	IV	0, 1000, 2000, 4000	> 4000
	10	PO	10000	-
Dog (Beagle)	1	IV	2000	> 2000
Monkey (cynomolgus)	1	SC	2000, 4000	> 4000
	1	IM	2000, 4000	> 4000
	1	IV	2000, 4000	> 4000

*1000 IU = 73.3 µg 2000 IU = 146.7 µg 4000 IU = 293.3 µg

There were no signs of local or systemic toxicity in any of the rat studies. In the dog study, there were no overt signs of toxicity following a single intravenous dose of 2000 IU/kg r-hFSH although there was evidence of transient liver toxicity following the administration of the control agent, u-hFSH. In the monkey studies, ovarian and endometrial changes were observed, but these findings are considered to be related to the pharmacological action of the compound.

Repeated Dose Toxicity

A total of seven repeated dose toxicity studies were performed with r-hFSH. These studies have been summarized below in Table 14.

Table 14: Repeated Dose Toxicity Studies with r-hFSH

Species (Strain)	#/Sex /Group	Route	Dose (IU/kg/day)	Duration (weeks)	Recovery Period
Rat (Sprague Dawley)	18	SC	**r-hFSH:** 0, 10, 30, 100 **u-hFSH:** 100	4	4
	15	SC	**r-hFSH:** 0, 300, 1000 **hMG:** 1000	4	2
	18	SC	**r-hFSH:** 0, 10, 100, 1000	13	4
Dog (Beagle)	2	IV	**r-hFSH:** 0, 20, 100 **u-hFSH:** 20, 100 **u-hFSH HP:** 20, 100	4	0
Monkey (Cynomolgus)	3 in the 10 & 30 IU/kg/day groups; 5 in all others	IM	**r-hFSH:** 0, 10, 30, 100 **u-hFSH:** 100	4	4
	5	IM	**r-hFSH:** 0, 300, 1000 **hMG:** 1000	4	2
	3 in the 10 & 100 IU/ kg/ day groups; 5 in all others	IM	**r-hFSH:** 0, 10, 100, 1000	13	4

* 10 IU = 0.7 µg 20 IU = 1.5 µg 100 IU = 7.3 µg 1000 IU = 73.3 µg

In rats, no treatment related mortalities or clinical signs of intolerance were observed. In the 4 week study at moderate doses, r-hFSH exerted a stimulatory effect on female gonads as evidenced by a number of morphological changes involving the ovaries, genital tract and mammary glands seen mainly in females given 30 and 100 IU/kg/day. These were related to the pharmacological activity of the hormone injected at high doses over a long period of time. In the 4 week study at high doses and in the 13-week study, atrophy of the gonads and secondary sex organs, predominantly in females, were seen. These findings could be related to inhibin production as well as to the inactivation of exogenous FSH by the high levels of antibodies to FSH which were found to have developed in the rats within four weeks of treatment as a consequence of the injection of a foreign protein. This is also in agreement with the fact that serum FSH levels decreased as treatment continued.

In the dog, the serum FSH levels measured during dosing confirmed extensive exposure thus the study was a valid test of the effects of r-hFSH. No mortalities were observed following administration of 20 or 100 IU/kg/day for 4 weeks. Body weight was unaffected by treatment and no signs of systemic toxicity or local reactions at the injection sites were seen. The predominant changes were related to the pharmacological activity of the compound on the reproductive systems of both the male and female animals. At the higher dose of 100 IU/kg/day, slight acute inflammation of the liver was also found in one of the treated females.

In the monkey, as in the dog, the serum FSH levels measured during dosing confirmed extensive exposure despite the development of antibodies to the foreign protein. The general similarity of the toxicological findings, which represent the pharmacological actions of high doses of FSH, in the shorter and longer term experiments demonstrate that some hormonal activity of FSH was still maintained.

No mortalities were observed in any of the monkey studies. Body weight was unaffected by treatment with r-hFSH; the predominant effects were those anticipated from the known pharmacodynamic actions of FSH. Despite the development of anti-FSH antibodies, r-hFSH caused prominent and continued but reversible ovarian stimulation resulting in cysts, some haemorrhagic, endometrial hyperplasia, even some proliferation of mammary glandular cells, and changes in the vagina. Hypertrophy of pituitary acidophilic cells was seen in females receiving r-hFSH at doses of 30 to 1000 IU/kg/day and thymus atrophy was seen at doses of 300 and 1000 IU/kg/day. At a dose of 100 IU/kg/day, r-hFSH caused some stimulation of testicular tubules and a possible increase in spermatogenesis. Slight acute inflammation of the liver was also found in one of the females given r-hFSH at a dose of 100 IU/kg/day.

In the various 4 week experiments, the hormonal actions were largely reversible, but the anatomical changes had progressed so far in the 13 week studies that complete recovery was not possible after the high doses (100 to 1000 IU/kg/day).

In the 4 week studies, it was not possible to determine a definite difference in potency between the SC and IM routes. The 'No observed (pharmacological) effect level' was probably about 10 IU/kg/day in the dog (dosed IV) and was less than 10 IU/kg/day in the monkey (IM) and rat (SC).

No conventional target organ toxicity was found in any species, apart from a possible low incidence of centrilobular inflammation in the liver in dogs at the highest dose of r-hFSH and both of two clinical preparations of u-hFSH, and minor changes in neutrophils, platelets and PTT, also in the same groups. The latter effects cannot be distinguished from normal concomitants of stimulated oestrus.

The findings in these experiments did not show any major difference between recombinant and natural urinary human FSH. Differences from the effects of hMG could be attributed to the LH activity of the latter preparation.

Mutagenicity

r-hFSH did not show any mutagenic activity in the range of mutagenicity studies conducted.

Reproduction and Teratology

Reproductive toxicology studies were conducted to assess the possible effects of r-hFSH on reproduction. Segments I, II, and III were conducted in rats by the SC route as this is the proposed therapeutic route in man. Segment II was also conducted in rabbits as a non-rodent species. The doses of r-hFSH used for all the studies were 5, 40, and 320 IU/kg/day in comparison with hMG at the dose of 320 IU/kg/day. The highest dose of r-hFSH was about 100 times the clinical dose and was expected to produce profound reproductive effects.

Given in a sufficiently high dose, r-hFSH was able to cause death and other forms of fetal effects in the rat and rabbit, but without being a teratogen. It also caused dystocia. Human Menopausal Gonadotropin (standardized to the same follicle stimulating activity but also possessing luteinizing activity) had the same effects. r-hFSH, 5 IU/kg/day SC, had no effect in the rat, and 40 and 320 IU/kg/day had progressively more severe actions. In general terms r-hFSH 320 IU/kg/day had the same activity as hMG 320/kg/day. The retardation of weight gain found in the Segment II test in rats given high doses of r-hFSH and hMG can be attributed to the resorptions produced. The rabbit was more sensitive than the rat, as even 5 IU/kg/day of r-hFSH caused death of almost all embryos in utero.

In the fertility study in the rat, r-hFSH at 40 and 320 IU/kg/day and hMG (320 IU/kg/day) both impaired fertility. As both sexes had been dosed before mating it is not known whether both females and males were affected, although it appears likely that females were affected, judging by the changes observed in the ovaries and the known physiological effects of FSH on follicular development and function. No histological changes were seen in the testes, even at the highest r-hFSH dose of 320 IU/kg/day, in spite of a small decrease in weight.

Other Studies

Although the local tolerance of r-hFSH was assessed in the acute and multidose toxicity studies, in which it was well tolerated on SC, IM and IV injection, a sensitization test in guinea pigs and a local tolerance study in rabbits were also performed.

In guinea pigs, r-hFSH was a sensitizer in the maximization test, but to a lesser degree than u-hFSH. In rabbits, a concentration of 600 IU/mL, administered SC and IM, was well tolerated. The finding of sensitization in guinea pigs is not surprising as both r-hFSH and u-hFSH are foreign proteins to this animal species. The repeated dose toxicity studies clearly demonstrated the formation of antibodies to human FSH when administered to animals. The greater purity of r-hFSH is most likely responsible for the milder response observed. These findings are not considered to be clinically relevant.

Together with the much more extensive evidence from the repeated dose toxicity studies, it can be concluded that r-hFSH is well tolerated at the site of administration.

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PART III: CONSUMER INFORMATION

GONAL-f® Pen
(follitropin alfa injection)

This information is part III of a three-part "Product Monograph" published when GONAL-f® Pen was approved for sale in Canada and is designed specifically for Consumers. This is only a summary and does not contain all information about GONAL-f® Pen. Contact your doctor or pharmacist if you have any questions about the drug.

This leaflet is designed to help you self-administer GONAL-f® solution for injection using the prefilled Pen and to answer many of the questions you may have on infertility and GONAL-f® therapy.

ABOUT THIS MEDICATION

What is GONAL-f®?
GONAL-f® is follicle-stimulating hormone (FSH) with no urinary proteins, which stimulates oocyte (egg) development in women. GONAL-f® is a highly purified recombinant human form of FSH, manufactured using the latest technology with proven effectiveness and safety in clinical studies.

It is provided in liquid formulation in the prefilled Pen, for easy administration under the skin (subcutaneous injection).

GONAL-f belongs to a group of medicines called "gonadotropins".

What is GONAL-f® used for?
GONAL-f® (follitropin alfa for injection) is used to stimulate the maturation of follicles in ovulatory patients undergoing Assisted Reproductive Technologies (ART) such as *in vitro* fertilization (IVF). To complete the maturation of follicles another hormone, hCG (human chorionic gonadotropin) is given.

GONAL-f® is also used to stimulate the maturation of follicles in some patients whose menstrual cycle is either irregular or absent. To complete the maturation of follicles another hormone, hCG is given.

When should GONAL-f® not be used?
GONAL-f® should **not** be used if you:

- Have high levels of FSH indicating primary ovarian failure
- Have uncontrolled thyroid or adrenal dysfunction
- Are allergic (hypersensitive) or have a history of hypersensitivity to FSH or to any of the other ingredients of GONAL-f®
- Are pregnant or breastfeeding
- Have ovarian enlargement or a cyst not due to polycystic ovarian disease (PCO)
- Have vaginal bleeding of unknown cause
- Have tumours of the ovary, uterus, breast or brain (hypothalamus or pituitary gland)

How is GONAL-f® administered?
Due to its high level of purity, GONAL-f® is approved for subcutaneous injection (just under the skin), which is easier and less painful than intramuscular injections (in the muscle). In fact, with professional guidance, you can learn to do your own injections in the comfort and privacy of your own home.

Why is GONAL-f® provided in the prefilled Pen?
GONAL-f® is provided in the prefilled pen to help you easily self-administer accurate and consistent GONAL-f®. It is designed so that it is easy to read and set the dosage dial confirmation before injecting the medication. The pen reservoir is clear so that the amount of medication available in the Pen can be seen at all times.

The medicinal ingredient in GONAL-f®:
Follitropin alfa.

The nonmedicinal ingredients of GONAL-f® are:
Poloxamer 188, sucrose, L-methionine, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, m-cresol, phosphoric acid, sodium hydroxide and water for injection.

This product does not contain latex.

What dosage forms of GONAL-f® are available?
GONAL-f® Pens are available as a solution in a cartridge pre-assembled in a multi-use disposable prefilled pen, ready to use.

GONAL-f® Pens are available in the following dosage forms:

- 300 IU/0.48 mL
- 450 IU/0.72 mL
- 900 IU/1.44 mL

WARNINGS AND PRECAUTIONS

General

To help avoid side effects and ensure proper use, talk to your doctor or pharmacist before you take GONAL-f®.

Your fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility disorders.

Porphyria
If you have porphyria or a family history of porphyria, GONAL-f® may increase the risk of an acute attack. Tell your doctor immediately if:

- Your skin becomes fragile and easily blistered, especially skin that has been frequently in the sun, and/or
- You have stomach, arm or leg pain.

In case of the above events your doctor may recommend that you stop treatment.

Overstimulation of the Ovary During FSH Therapy

Ovarian Enlargement

Use of FSH therapy to stimulate follicular development may result in the growth of more than one follicle. This may result in mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distention and/or abdominal pain. It is more commonly seen in women with polycystic ovarian syndrome.

Ovarian Hyperstimulation Syndrome (OHSS)

Treatment increases your risk of developing ovarian hyperstimulation syndrome (OHSS). This is when multiple follicles develop and may become large cysts. In rare cases, severe OHSS may be life-threatening. OHSS may cause fluid build-up in your abdominal and chest areas and can cause blood clots to form. Call your doctor right away if you notice severe abdominal swelling, pain in the stomach area (abdomen), feeling sick (nausea), vomiting, sudden weight gain due to fluid build-up, diarrhea, decreased urine output or trouble breathing. However, if you follow your doctor's instructions for the recommended dose and schedule of administration, the occurrence of OHSS is uncommon. GONAL-f® treatment seldom causes significant OHSS unless the medicine used to induce final follicular maturation and ovulation (containing human chorionic gonadotropin - hCG) is administered. In cases where OHSS is developing it is recommended to not give hCG, and women should prevent pregnancy at this time by not having sexual intercourse.

Breathing and Blood Clotting

Serious breathing problems (e.g., lung collapse, extreme shortness of breath and worsening of asthma) have been reported with use of gonadotropin therapy.

Treatment with gonadotropin therapy may increase the risk of having a blood clot (thrombosis) which may or may not be associated with Ovarian Hyperstimulation Syndrome. Blood clots can lead to serious medical conditions, such as blockage in the lungs (pulmonary embolus), blood vessel problems (thrombophlebitis), heart attack, stroke, blockage in the arteries in your arms and legs which may result in a loss of your arm or leg. In rare cases, lung complications and/or blood clots have resulted in death.

Reproductive Issues

Since women with infertility undergoing assisted reproduction, particularly IVF, may have tubal abnormalities, the incidence of ectopic pregnancies (pregnancy in the fallopian tubes) might be increased. Early ultrasound to confirm that a pregnancy is in the uterus is important.

Miscarriages may be higher than in the normal population, but comparable with the rates found in women with fertility problems.

Reports of multiple births have been associated with fertility treatments. You should discuss the potential risk of multiple births with your doctor before beginning treatment.

The incidence of multiple births with GONAL-f® is no different from any other gonadotropin and is dependent upon the protocol used by the clinic. Your doctor will monitor you closely to help minimize the possibility of a multiple pregnancy. The majority of births (about 80%) are single babies. Of those women who do have multiple births, the majority of these are twins. Only very few women conceive 3 or more babies. Even so, neither single nor multiple births can be guaranteed.

There have been reports of ovarian and other reproductive systems tumours in women who have had infertility treatment. It is not known if treatment with fertility medicines increase the risk of these tumours in infertile women.

INTERACTIONS WITH THIS MEDICATION

GONAL-f® is often used with other medicines to stimulate ovulation (e.g, hCG and LH), and may help the maturation of follicles which contains the eggs. If a GnRH agonist or antagonist medicine is also given along with your GONAL-f® in your treatment program, you may be told by your doctor to change your dose of GONAL-f® over the course of your treatment. No other significant interactions with other medicines have been reported.

PROPER USE OF THIS MEDICATION

Understandably, you may be a little anxious at first about giving yourself an injection. That is why this information has been produced. Refer to it as necessary and follow each instruction step by step.

Always take GONAL-f® exactly as your doctor has instructed you. You should check with your health care provider if you are unsure.

Before starting to use your pen, please read these instructions the whole way through first. This pen has been prescribed for you – do not let anyone else use it. The numbers on the dose display are measured in International Units or IU. Your doctor would have told you how many IUs to inject each day. Give yourself the injection at the same time each day.

Recommended Dose

Every treatment is individualized. Your treatment has been carefully designed for you by your doctor. Over the course of your treatment, doses may range between 75 to 450 IU depending on your specific medical condition and your response to the medicine.

The GONAL-f® Pens have been designed to allow simple and flexible dosing that covers most treatment protocols or dosing regimens.

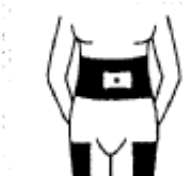
Overdosage:

If you have accidentally injected too much GONAL-f®, do not panic. Simply contact your physician or healthcare professional for further instructions.

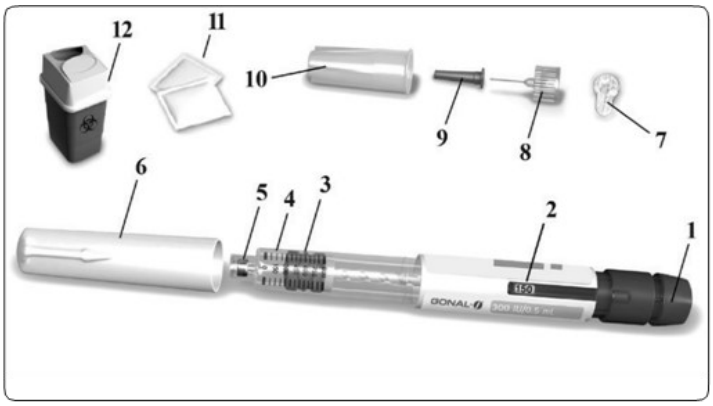
Missed dose

What should I do if I forget to take my GONAL-f®?
Do not take a double dose to make up for any doses you have missed. Contact your doctor for advice if you forget to take a dose of GONAL-f®.

Where should I inject GONAL-f®?
The most easily accessible areas for subcutaneous injection are the abdomen and thighs. The absorption of GONAL-f® is the same regardless of the injection site selected. You may find the injection is more comfortable if you vary the site each time you inject GONAL-f®.



GONAL-f® Pen, and other materials you may need for injection:



1. Dose setting knob
2. Dose Display
3. Plunger piston
4. Reservoir holder
5. Threaded needle connector
6. Pen cap
7. Peel-off seal tab
8. Removable needle
9. Inner needle shield
10. Outer needle cap
11. Alcohol swabs
12. Sharps disposal container

1. Before you start using your GONAL-f® Pen:

- Wash your hands with soap and water. It is important that your hands and items you use be as clean as possible.

- Take the carton out of the refrigerator for at least 30 minutes before use to let it warm to room temperature. Do not use a microwave or other heating element to warm up the pen.

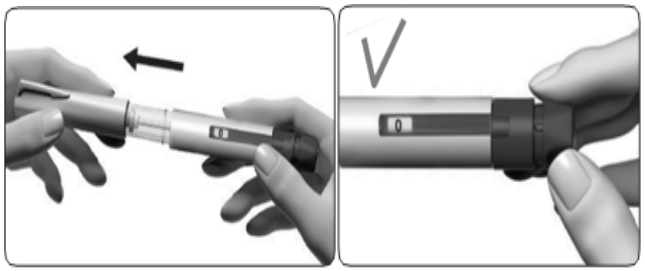
  Warning: Do not shake the pen, as this may cause air bubbles to appear in the medication.

- On a clean surface, e.g., clean table or kitchen surface, lay out everything you will need:
  - GONAL-f® Pen
  - One removable injection needle (1/2 inch 29 gauge) [use the single-use disposable needles provided with the GONAL-f® Pen box].
  - Alcohol swabs
  - Sharps disposal container

- Verify the **expiration date** on the pen label. Do not use expired medication.

2. Getting your GONAL-f® Pen ready for injection

- Take off the pen cap.
- Wipe the end of the threaded tip (containing the rubber center) using an alcohol swab.
- Look carefully at the reservoir holder. Check that the reservoir holder is not cracked and that the solution is clear and does not contain particles. If the reservoir holder is cracked or if the solution is discoloured or cloudy, obtain a new pen.
- Verify that the Dose Display is set to "0".



- Prepare your needle for injection:
  - Get a new needle – only use the "single-use" needles supplied
  - Hold the outer needle cap firmly
  - Check that the peel-off seal on the outer needle cap is not damaged or loose:

Example of a good seal

Example of a bad seal

- Remove the peel-off seal

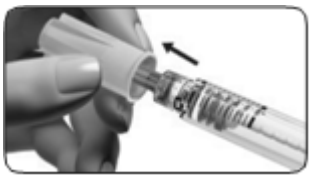
CAUTION: If the peel-off seal is damaged or loose, do not use the needle. Throw it away in a sharps disposal container. Get a new needle.

3. Attach the needle

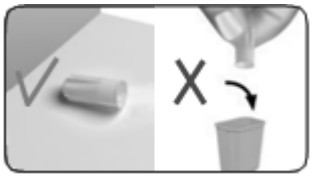
- Screw the threaded tip of the GONAL-f® Pen into the outer needle cap until you feel a light resistance.

  - Important Note: Do not attach the needle too tightly; the needle could be difficult to remove after the injection.

- Remove the outer needle cap by pulling it straight off.



- Put it aside for later use.
- Do not throw away the outer needle cap; you will need it for removing the needle from the pen.



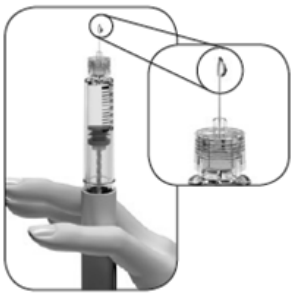
- Hold the GONAL-f® Pen with the needle pointing upwards.

- Carefully remove the green inner shield by pulling it straight off and discard it.
  - Warning: Do not recap the needle with the green inner shield as this can lead to needle stick.

- **Please note: if this is NOT a brand new GONAL-f® Pen (you have done previous injections with this pen), then proceed to Section 4: "Setting the dose prescribed by your doctor".**

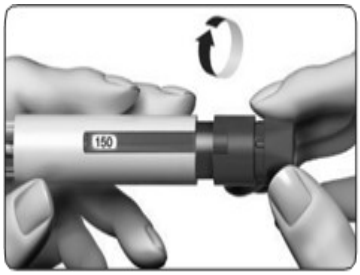
- **If this IS A BRAND NEW PEN that you are using for the first time**, look closely at the tip of the needle for a tiny drop of fluid.
  - If you see a tiny drop(s) of fluid, proceed to Section 4 "Setting the dose prescribed by your doctor".
  - If you do not see a tiny drop(s), please refer to Section 7 "Preparing your new GONAL-f® Pen for first time use".

- **Important Note: Only check for drop(s) with a brand new pen. This step is not required if you are doing additional injections using the same pen.**

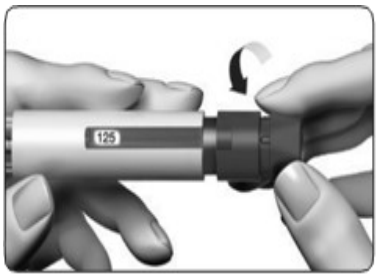


4. Setting the dose prescribed by your doctor

- Turn the dose setting knob forward (or clockwise) until your prescribed dose shows in the Dose Display. Do not push or pull the dose setting knob while you turn it.
  - In this example below, it is 150 IU.



- If you have turned the knob past your prescribed dose, turn the knob backwards (or counter-clockwise) to correct the dose.

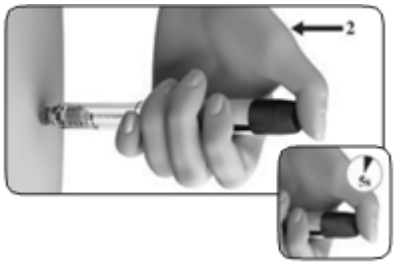


- Important Note: Check that the Dose Display shows your prescribed dose before you move on to the next step.

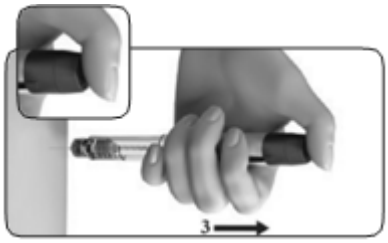
5. Injecting the dose

- Choose an injection site in the area your doctor or nurse has told you to give the injection.
    - Note: To minimize skin irritation, select a different injection site each day. See section "Where should I inject GONAL-f®?" for more details.
- Clean the skin by wiping the area with an alcohol swab. Allow the site to dry.
- Set the alcohol wipe to the side.
- Verify once more that the Dose Display is showing the correct dose. If it is not the correct dose, you must adjust it by turning the dose setting knob either clockwise or counter-clockwise (see Step 4 "Setting your dose prescribed by your doctor").
- Inject the dose as you were trained to do by your doctor or nurse.
    - Holding the pen in one hand, use your other hand to gently squeeze the skin together to make a raised area at the injection site.
    - Insert the needle at a 90° angle into the skin. You might bend the needle if you do not insert it at a 90° angle.
    - Press the dose knob down as far as it will go and hold it to complete the full injection.

- Hold the dose knob down for a minimum of 5 seconds to ensure you inject the full dose. The larger the dose, the longer it will take to inject.



- **Do not release the dose setting knob until you remove the needle from your skin.**



- Remove the needle from your skin, release the dose setting knob.
- The dose number shown in the Dose Display will turn back to 0 to indicate that the complete dose was delivered. If you see a number higher than 0, proceed to Section 6 "After the Injection – Complete a Partial Injection" (only when needed).
- Use the clean side of your alcohol swab to gently clean the injection site. If there is minor oozing you may need to apply a small amount of pressure for a few seconds.

6. After the injection

- Verify you have given a complete injection.
- Check that the Dose Display shows 0.

Important Note: If the Dose Display shows a number higher than 0, the GONAL-f® Pen is empty and you have not received your full prescribed dose.

Complete a Partial Injection (only when needed):

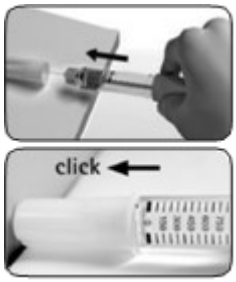
- The Dose Display will indicate the missing amount (in the example below, it is 50 IU), you need to inject using a new pen.

- Repeat Section 1 "Before you start using your GONAL-f® Pen" through Section 2 "Getting your GONAL-f® Pen ready for injection" with a second pen.
- **For a brand new pen that you are using for the first time**, look closely at the tip of the needle for a tiny drop of fluid.
    - If you see a tiny drop(s) of fluid, proceed to Section 4 "Setting the dose prescribed by your doctor".
    - If you do not see a tiny drop(s), please refer to Section 7 "Preparing your new GONAL-f® Pen for first time use".
- Once your pen is ready, set the dose as described in Section 4 to the missing amount indicated in the Dose Display on your previous pen. Complete your prescribed dose by following steps outlined in Section 5 "Injecting the dose".

Important Note: Always make sure to use a new needle for each injection.

Removing the needle after each injection:

- Place the outer needle cap on a flat surface.
- Hold the GONAL-f® Pen firmly with one hand, and slip the needle into the outer needle cap. Be careful not to prick yourself with the needle.
- Continue by pushing the capped needle against a firm surface until you hear a "click."

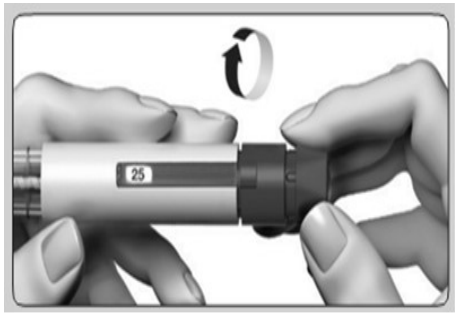


- Grip the outer needle cap and unscrew the needle by turning counter clockwise. Dispose of the used needle safely.

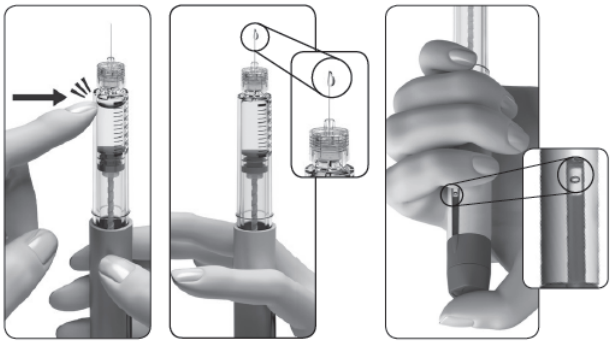
- Never reuse any used needle. Never share needles.
- Please note: your clinic may provide you with a special sharps container designed for GONAL-f®. If you have received the special GONAL-f® sharps container, simply follow the steps to remove the needle that are outlined on the box.
- Recap the pen.

7. Preparing your new GONAL-f® Pen for first time use

- If you do not see a tiny drop(s) at or near the needle tip the first time you use a new pen, you must perform the steps below:
    - Gently turn the dose setting knob clockwise until it reads 25 in the Dose Display. You can turn the dose knob backwards if you turn it past 25.



- Hold the pen with the needle pointing upward.
- Tap the reservoir holder gently.
- Press the dose setting knob as far as it will go. A tiny drop of fluid will appear at the tip of the needle. The amount of fluid seen at the needle tip is part of the overfill from the pre-filled pen.
- Verify that the Dose Display reads "0".



- You may need to repeat this step if you do not see a tiny drop of liquid appearing at the tip of the needle.
- Proceed to Section 4 "Setting the dose prescribed by your doctor".

Storing the GONAL-f® Pen:

CAUTION: Never store the pen with the needle attached. Always remove the needle from the GONAL-f® Pen before replacing the pen cap.

- Store the pen in its original packaging in a safe place
- When the pen is empty, ask your pharmacist how to dispose of it.

Important Note: Medicine should not be disposed of via wastewater or household waste.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Are there any side effects with gonadotropin therapy?
Fertility drugs are safe to take with close monitoring by your doctor. As with all medication, there is a potential for side effects.

The following side effects have been reported with the use of GONAL-f® during clinical trials and post-market use:

Common and Very Common: may affect 1 to 10 users in 100
- Ovarian cysts
- Mild to moderate ovarian enlargement
- Breast tenderness
- Mild to moderate OHSS
- Mild to severe injection site reaction (such as pain, redness, bruising, swelling and/or irritation)
- Headache
- Stomach pain or bloating
- Feeling sick (nausea), vomiting, diarrhea

Uncommon, Rare and Very Rare: may affect less than 1 to 10 users in 1,000
- Severe OHSS
- Blood clots (thrombosis)
- Difficulty breathing (acute pulmonary distress)
- Worsening of asthma
- Mild to severe allergic reactions (hypersensitivity) such as rash, red skin, hives, swelling of your face with difficulty breathing may occur. These reactions can sometimes be serious.

The greatest concern your doctor will have is ovarian hyperstimulation syndrome (OHSS). To avoid the development of OHSS, your doctor will carefully monitor your response to GONAL-f®. Ovarian enlargement, sometimes accompanied by abdominal bloating and pain, may occur in about 20% of women taking gonadotropins. This is generally reversed with cessation of treatment and severe life-threatening cases are rare.

A causal relationship between treatment with fertility drugs and ovarian cancer has not been established.

The following medical events have been reported subsequent to pregnancies resulting from gonadotropin therapy in controlled clinical trials: spontaneous abortion, tubal pregnancy, premature labour, postpartum fever and congenital abnormalities.

None of events were thought to be drug-related. The incidence is not more than that found in the general population.

This is not a complete list of side effects. If you experience any unusual symptoms or side-effects while taking GONAL-f® Pen, you should report them to your doctor or pharmacist immediately. It is also wise to discuss the possibility of side effects with your doctor before you begin treatment.

HOW TO STORE IT

GONAL-f® Pen may be stored by the patient between 2 and 25°C (in the refrigerator or at room temperature) for a single period of not more than 3 months. After first use, the pen may be stored at 25°C (room temperature) for a maximum of 28 days.

Do not use the GONAL-f® Pen if the solution contains particles or is not clear.

Do not freeze. Protect from light.

Keep in a safe place out of the reach of children.

Do not use after the expiry date.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:
- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Report Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at: www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full Product Monograph, prepared for health care professionals can be obtained from:

EMD Serono, A Division of EMD Inc., Canada
2695 North Sheridan Way, Suite 200
Mississauga ON L5K 2N6
A Business of Merck KGaA, Darmstadt, Germany

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