N1973801G

MERCK

GONAL-f® 75 IU

Powder and solvent for solution for injection

Ingredient:

Active ingredient: follitropin alfa

Follitropin alfa is recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary cells by recombinant DNA technology.

Composition

Each vial contains 5.5 micrograms of follitropin alfa equivalent to 75 IU (International Units). Each ml of the reconstituted solution contains 75 IU.

Clinical Properties

Indications

Women

Anovulation including polycystic ovarian syndrome in women who have been unresponsive to treatment with clomiphene citrate.

Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT).

Men

Stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy.

Dosage and administration

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

Posology

The dose 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 medicinal products. It is advised to adhere to the recommended starting doses indicated below.

Comparative clinical studies have shown that on average patients require a lower cumulative dose and shorter treatment duration with GONAL-f compared with urinary FSH. Therefore, it is considered appropriate to give a lower total dose of GONAL-f than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation.

Women with anovulation (including polycystic ovarian syndrome)

GONAL-f may be given as a course of daily injections. In menstruating women treatment should commence within the first 7 days of the menstrual cycle.

A commonly used regimen commences at 75 - 150 IU FSH daily and is increased preferably by 37.5 or 75 IU at 7 or preferably 14 day intervals if necessary, to obtain an adequate, but not excessive, response. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and/or oestrogen secretion. The maximal daily dose is usually not higher than 225 IU FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should undergo further evaluation after which she may be recommence the treatment at a higher starting dose than in the abandoned cycle.

When an optimal response is obtained, a single injection of 250 micrograms recombinant human choriogonadotropin alfa (r-hCG) or 5,000 IU, up to 10,000 IU hCG should be administered 24 - 48 hours after the last GONAL-f injection. The patient is recommended to have coitus on the day of, and the day following, hCG administration. Alternatively intrauterine insemination (IUI) may be performed.

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dosage lower than that of the previous cycle.

Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other assisted reproductive technologies

A commonly used regimen for superovulation involves the administration of 150 - 225 IU of GONAL-f daily, commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum oestrogen concentration and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU daily. In general adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days).

A single injection of 250 micrograms r-hCG or 5,000 IU up to 10,000 IU hCG is administered 24 - 48 hours after the last GONAL-f injection to induce final follicular maturation.

Down-regulation with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. In a commonly used protocol, GONAL-f is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks of treatment with an agonist, 150 - 225 IU GONAL-f are administered for the first 7 days. The dose is then adjusted according to the ovarian response.

Overall experience with in IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

Men with hypogonadotrophic hypogonadism

GONAL-f should be given at a dose of 150 IU three times a week, together with hCG, for a minimum of 4 months. If after this period, the patient has not responded, the combination treatment may be continued; current clinical experience indicates that treatment for at least 18 months may be necessary to achieve spermatogenesis.

Administration

GONAL-f is intended for subcutaneous administration. The injection site should be alternated daily.

Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and have access to expert advice. If you administer GONAL-f yourself, please carefully read and follow the 'Instructions for use' provided at the end of this package insert.

- GONAL-f must be administered immediately after preparation.
- The first injection of GONAL-f should be given under supervision of your doctor.
- Your doctor or nurse will show you how to inject GONAL-f before you can inject yourself.

Contraindications

- Allergy (hypersensitivity) to the active ingredient follitropin alfa, FSH or to any of the excipients (see section 'Excipient' above)
- Tumours of the hypothalamus or pituitary gland
- Large ovaries or sacs of fluids within the ovaries (ovarian cyst) not due to polycystic ovarian syndrome
- Unexplained vaginal bleeding (gynaecological haemorrhages of unknown aetiology)
- Cancer in the ovaries, uterus or breasts

Gonal-f must not be used when an effective response cannot be obtained, such as:

- Primary ovarian failure
- Malformations of sexual organs incompatible with pregnancy
- Fibroid tumours of the uterus incompatible with pregnancy
- Primary testicular insufficiency

Do not use GONAL-f if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before using this medicine.

Special warnings and precautions

GONAL-F is a potent ganadotrophic substance capable of causing mild to severe adverse reactions, and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, as well as the availability of appropriate monitoring facilities. In women, safe and effective use of GONAL-f calls for monitoring of ovarian response with ultrasound, alone or preferably in combination with measurement of serum oestradiol levels, on a regular basis. There may be a degree of interpatient variability in response to FSH administration, with a poor response to FSH in some patients and exaggerated response in others. The lowest effective dose in relation to the treatment objective should be used in both men and women.

Porphyria

Tell your doctor before you start treatment, if you or any member of your family have porphyria (an inability to break down porphyrins that may be passed on from parents to children) as GONAL-f may increase the risk of an acute attack. Patients with porphyria or a family history of porphyria should be closely monitored during treatment with GONAL-f. Deterioration or a first appearance of this condition may require cessation of treatment.

Tell your doctor straight away 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.

Treatment in women

Before starting treatment, the couple's infertility should be assessed as appropriate. It is recommended that GONAL-f is not used in conditions where an effective response cannot be expected, such as primary ovarian failure, malformation of the sexual organs incompatible with pregnancy or fibroid tumours of the uterus usually considered incompatible with pregnancy. Prior to the treatment patients should also be evaluated for hypothyroidism, adrenocortical deficiency and hyperprolactinaemia and appropriate specific treatment should be given.

Patients undergoing stimulation of follicular growth, whether as treatment for anovulatory infertility of ART procedures, may experience ovarian enlargement or develop hyperstimulation. Adherence to recommended GONAL-f dose and regimen of administration, and careful monitoring of therapy will minimise the incidence of such events. For accurate interpretation of the indices of follicle development and maturation, the physician should be experienced in the interpretation of relevant tests.

In clinicals trials, an increase of the ovarian sensitivity to GONAL-f was shown when administrated with lutropin alfa. If an FSH dose increae is deemed appropriate dose adaption should preferably be at 7-14 day intervals and preferably with 37.5-75 IU increments.

No direct comparison of GONAL-f/LH versus human menopausal gonadotropin (hMG) has been performed. Comparison with historical rate suggest that the ovulation rate obtained with GONAL-f /LH is similar to that obtained with hMG.

Ovarian Hyperstimulation Syndrome (OHSS)

This medicine increases your risk of developing OHSS. This is when your follicles develop too much and become large cysts. If the recommended dose and schedule of administration are adhered to, the occurrence of OHSS is less likely.

Talk to your doctor straight away if you get lower abdominal pain, gain any weight rapidly, feel sick or are vomiting or if you have difficulty in breathing. Your doctor might ask you to stop using this medicine (see section 'Adverse reactions').

GONAL-f treatment seldom causes severe OHSS unless the medicine that is used for final follicular maturation (containing hCG) is administered. If you are developing OHSS your doctor may not give you any hCG in this treatment cycle and you may be told not to have sex or to use a barrier contraceptive method for at least four days.

A certain degree of ovarian enlargement is an expected effect of controlled ovarian stimulation. It is more commonly seen in women with polycystic ovarian syndrome and usually regresses without treatment.

In distinction to uncomplicated ovarian enlargement, OHSS is a condition that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

Mild manifestations of OHSS include abdominal pain, abdominal discomfort and distension, and enlarged ovaries. Moderate OHSS may additionally present with nausea, vomiting, ultrasound evidence of ascites and marked ovarian enlargement.

Severe OHSS further includes symptoms such as abdominal pain, abdominal distension, severe pvarian enlargement, weight gain, dyspnoea or oligouria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal signs such as hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, or acute pulmonary distress. Rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events, such as pulmonary embolism, ischaemic stroke or myocardial infarction.

Independent risk factors for developing OHSS include young age, lean body mass, polycystic ovarian syndrome, high doses of exogenous gonadotropins, high absolute or rapidly rising serum oestradiol levels (e.g. >900 pg/ml or >3,300 pmol/l in anovulation; >3,000 pg/ml or >11,000 pmol/l in ART) and previous episodes of OHSS, large number of developing ovarian follicles (e.g. ≥ 3 follicles of ≥ 14mm in diameter in anovulation; ≥ 20 follicles of ≥ 12 mm in diameter in ART).

Adherence to recommended GONAL-f dose and regimen of administration can minimise the risk of ovarian hyperstimulation. Monitoring of stimulation cycles by ultrasound scans as well as oestradiol measurements are recommended to early identify risk factors.

There is evidence to suggest that hCG plays a key role in triggering OHSS and that the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, if signs of ovarian hyperstimulation occur such as serum oestradiol level > 5,500 pg/ml or >20,200 pmol/l and/or ≥ 40 follicles in total, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or use barrier contraceptive methods for at least 4 days. As OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event, it most often occurs after hormonal treatment has been discontinued and reach its maximum at about 7 to 10 days following treatment. Therefore, patients should be followed for at least two weeks after hCG administration.

In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation. Mild or moderate OHSS usually resolves spontaneously. If severe OHSS occurs, it is recommended that gonadotropin treatment be stopped if still ongoing, and that the patient be hospitalised and appropriate therapy be started.

Multiple pregnancy

When using GONAL-f, you have a higher risk of being pregnant with more than one child at the same time ('multiple pregnancy', mostly twins), than if you conceived naturally. Multiple pregnancy may lead to medical complications for you and your babies, carries an increased risk of adverse maternal and perinatal outcomes.

To minimise the risk of multiple pregnancy, careful monitoring of ovarian response is recommended.

When undergoing ART the risk of having a multiple pregnancy is mainly related to your age, the quality and the number of fertilised eggs or embryos placed inside you. The patients should be advised of the potential risk of multiple births before starting treatment.

Pregnancy loss

When undergoing ART or stimulation of your ovaries to produce eggs (follicular growth), you are more likely to have a miscarriage than the average woman.

Ectopic pregnancy

Women with a history of tubal disease are at risk of ectopic pregnancy (pregnancy outside the uterus), whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after ART, was reported to be higher than in the general population.

Reproductive system neoplasms

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility treatment. It is not yet established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women.

Congenital anomalies

The prevalence of congenital malformations (birth defects) after ART may be slightly higher than after spontaneous conceptions. This could be due to parental factors (e.g. maternal age, sperm characteristics) ART procedures and multiple pregnancies.

Thromboembolic events

In women with recent or ongoing thromboembolic disease (blood clots in the leg or in the lung, or a heart attack or stroke) or women with generally recognised 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 carry an increased risk of thromboembolic events.

Treatment in men

To monitor the treatment, your doctor may ask you to provide semen for analysis 4 - 6 months after starting treatment.

Elevated endogenous FSH levels are indicative of primary testicular failure. Such patients are unresponsive to GONAL-f/hCG therapy. Gonal-f should not be used when an effective response cannot be obtained.

Sodium Content

GONAL-f contains less than 1mmol sodium (23mg) per dose, i.e. essentially "sodium-free".

Interactions

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Concomitant use of GONAL-f with other agents used to stimulate ovulation (e.g. hCG, clomiphene citrate) may potentiate the follicular response, whereas concurrent use of a GnRH agonist or antagonist to induce pituitary desensitisation may increase the dosage of GONAL-f needed to elicit an adequate ovarian response.

Pregnancy and lactation

Pregnancy

There is no indication for the use of GONAL-f during pregnancy.

Data on a limited number of exposed pregnancies indicate no adverse reactions of gonadotropins on pregnancy, embryonal or foetal development, parturition or postnatal development following controlled ovarian stimulation.

No teratogenic effect has been observed in animal studies. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of GONAL-f.

Lactation

GONAL-f is not indicated during lactation. During lactation, the secretion of prolactin can result in a poor prognosis to ovarian stimulation.

Adverse reactions

Summary of the safety profile

The common adverse reactions are headache, ovarian cysts, and local reactions at the injection site, such as pain, redness, bruising, swelling or irritation. The mild to moderate of Ovarian Hyperstimulation Syndrome (OHSS) is common but the severe OHSS is uncommon.

The following definitions apply to the frequency terms used hereafter:

- very common (affects more than 1 user in 10)
- common (affects 1 to 10 users in 100)
- uncommon (affects 1 to 10 users in 1,000)
- rare (affects 1 to 10 users in 10,000)
- very rare (affects less than 1 user in 10,000)

Adverse reactions in women

Immunological disease

Very rare: mild to severe allergic reaction including systemic allergic reaction and shock

Neurological disease

- Very common: headache

Vascular disease

- Rare: Thromboembolic

Breathing, chest and mediastinal

- Very rare: Asthma deterioration

Gastrointestinal disease

- Common: abdominal pain, abdominal discomfort and distension, nausea, vomiting and diarrhoea

Reproductive system and breast disease

- Very common: ovarian cysts
- Common: mild to moderate OHSS and related symptoms
- Uncommon: severe OHSS and related symptoms
- Rare: severe complication of OHSS

General disease and local reactions at the injection site

- Very common: local reactions at the injection site such as pain, redness, bruising, swelling or irritation

Adverse reaction in men

Immunological disease

- Very rare: mild to severe allergic reaction including systemic allergic reaction and shock

Breathing, chest and Mediastinal

- Very rare: asthma deterioration

Skin and subcutaneous tissue disease

- Common: acne

Reproductive system and breast disease

- Common: Gynecomastia, varicocele

General disease and local reactions at the injection site

- Very common: local reactions at the injection site such as pain, redness, bruising, swelling or irritation

Investigation

Common: weight gain

Overdose

The effects of an overdose of GONAL-f are unknown, nevertheless there is a possibility that OHSS may occur, which is further described in section 'Special warnings and precautions' above.

Pharmacodynamic properties

GONAL-f contains a medicine called 'follitropin alfa'. Follitropin alfa is a type of 'Follicle Stimulating Hormone' (FSH) which belongs to the family of hormones called 'gonadotropins'. Gonadotropins are involved in reproduction and fertility.

Pharmacodynamics

Pharmacotherapeutic group: Sex hormones and modulators of the genital systems, gonadotropins,

ATC code: G03GA05.

In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles. In women with anovulation, the object of GONAL-f therapy is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of human Chorionic Gonadotropin (hCG).

Clinical efficacy and safety in women

In clinical trials, patients with severe FSH and LH deficiency were defined by an endogenous serum LH level < 1.2 IU/l as measured in a central laboratory. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

In clinical studies comparing r-hFSH and urinary FSH in assisted reproductive technologies (ART) and in ovulation induction, GONAL-f was more potent than urinary FSH in terms of a lower total dose and a shorter treatment period needed to trigger follicular maturation. In ART, GONAL-f at a lower total dose and shorter treatment period than urinary FSH, resulted in a higher number of oocytes retrieved when compared to urinary FSH.

Table: Results of study GF 8407 (randomised parallel group study comparing efficacy and safety of GONAL-f with urinary FSH in assisted reproduction technologies)

	GONAL-f (n = 130)	urinary FSH (n = 116)
Number of oocytes retrieved	11.0 ± 5.9	8.8 ± 4.8
Days of FSH stimulation required	11.7 ± 1.9	14.5 ± 3.3
Total dose of FSH required (number of FSH 75 IU ampoules)	27.6 ± 10.2	40.7 ± 13.6
Need to increase the dose (%)	56.2	85.3

Differences between the 2 groups were statistically significant ($p < 0.05$) for all criteria listed.

Clinical efficacy and safety in men

In men deficient in FSH, GONAL-f administered concomitantly with hCG for at least 4 months induces spermatogenesis.

Pharmacokinetics

Pharmacokinetic characteristics of GONAL-f are essentially similar to the pharmacokinetic characteristics of native human FSH.

Absorption: Following subcutaneous administration, the absolute bioavailability is about 70%. Following repeated administration, follitropin alfa accumulates 3 fold achieving a steady state within 3 – 4 days.

Distribution: Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and eliminated from the body with a terminal half-life of about one day. The steady state volume of distribution and total clearance are 10 l and 0.6 l/h, respectively.

Elimination: One-eighth of the follitropin alfa dose is excreted in the urine.

Non-clinical safety data

Based on conventional studies of single and repeated dose toxicity and genotoxicity non-clinical data reveal no special hazard for humans additional to that already stated in other sections of this document.

With respect to carcinogenicity, no *in vivo* studies have been conducted with follitropin alfa due to essential similarity of r-hFSH to the native human FSH. No carcinogenic risk is anticipated from the therapeutic use of GONAL-f.

Impaired fertility has been reported in rats exposed to pharmacological doses of follitropin alfa (≥ 40 IU/kg/day) for extended periods, through reduced fecundity.

Given in high doses (≥ 5 IU/kg/day) follitropin alfa caused a decrease in the number of viable foetuses without being a teratogen, and dystocia similar to that observed with urinary Menopausal Gonadotropin (hMG). However, since GONAL-f is not indicated in pregnancy, these data are of limited clinical relevance.

Pharmaceutical particulars

Excipients: sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, methionine, polysorbate 20, concentrated phosphoric acid and sodium hydroxide.

Solvent: Water for injections.

Incompatibilities

GONAL-f must not be administered as a mixture with other medicinal products in the same injection, except lutropin alfa or combination of lutropin alfa and follitropin alfa for which studies have shown that co-administration does not significantly alter the activity, stability, pharmacokinetic nor pharmacodynamic properties of the active substances.

Gonal-f can combine lutropin alfa for injection. Solve lutropin alfa first and then mix with Gonal-f powder.

Storage and stability

Do not store above 25°C. Store in the original package, in order to protect from light.

Do not use GONAL-f if you notice any visible signs of deterioration, if the liquid contains particles or is not clear.

Do not use after the expiry date.

Keep medicines out of the reach of children.

Presentations

GONAL-f 75 IU (water for injection in pre-filled syringe):

GONAL-f is supplied in packs of 1 vials of powder with the corresponding number of solvent in pre-filled syringes.

Instructions for use

This section tells you how to prepare and use your GONAL-f powder and solvent.

Before starting the preparation, please read these instructions the whole way through first.

Give yourself the injection at the same time each day.

1. Wash your hands and find a clean area

- It is important that your hands and the items you use be as clean as possible.
- A good place is a clean table or kitchen surface.

2. Get together everything you need and lay them out:

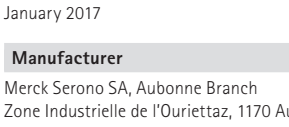
- 1 pre-filled syringe containing the solvent (the clear liquid)
- 1 vial containing GONAL-f (the white powder)
- 1 needle for preparation
- 1 fine bore needle for injection under the skin

Not provided in the pack:

- 2 alcohol swabs
- 1 sharp container

3. Preparing the solution

- Remove the protective caps from the powder vial and from the pre-filled syringe.
- Attach the needle for preparation to the pre-filled syringe, insert it into the powder vial and slowly inject all the solvent. Swirl gently without removing the syringe. Do not shake.
- Check that the resulting solution is clear and does not contain any particles.
- Turn the vial upside down and gently draw the solution back into the syringe by pulling the plunger.
- Remove the syringe from the vial and set it down carefully. Do not touch the needle and do not allow the needle to touch any surface.



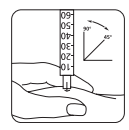
(If you have been prescribed more than one vial of GONAL-f, slowly re-inject the solution into another powder vial, until you have the prescribed number of powder vials dissolved in the solution. If you have been prescribed lutropin alfa in addition to GONAL-f, you may also mix the two medicines as an alternative to injecting each product separately. After dissolving the lutropin alfa powder, draw the solution back into the syringe and re-inject it into the vial containing GONAL-f. Once the powder has dissolved, draw the solution back into the syringe. Inspect for particles as before, and do not use if the solution is not clear. Up to three containers of powder may be dissolved in 1 ml of solvent.)

4. Getting ready the syringe for injection

- Change the needle for the fine bore needle.
- Remove any air bubbles: If you see air bubbles in the syringe, hold the syringe with the needle pointing upwards and gently flick the syringe until all the air collects at the top. Push the plunger until the air bubbles are gone.

5. Injecting the dose

- Immediately inject the solution: Your doctor or nurse will have already advised you where to inject (e.g. tummy, front of thigh). To minimise skin irritation, select a different injection site each day.
- Clean the chosen skin area with an alcohol swab using a circular motion.
- Firmly pinch the skin together and insert the needle at a 45° to 90° angle using a dart-like motion.
- Inject under the skin by pushing gently the plunger, as you were taught. Do not inject directly into a vein. Take as much time as you need to inject all the solution.
- Immediately withdraw the needle and clean the skin with an alcohol swab using a circular motion.



6. After the injection

- Dispose of all used items: Once you have finished your injection, immediately discard all needles and empty glass containers safely preferably in the sharp container. Any unused solution must be discarded.

Date of information

January 2017

Manufacturer

Merck Serono SA, Aubonne Branch

Zone Industrielle de l'Ouriettaz, 1170 Aubonne, Switzerland.

Solvent

Merck Serono S.p.A.

Via Delle Magnolie 15, Zona Industriale di Modugno, 70026 Modugno, Italy.

果納芬®75國際單位（5.5微克）

GONAL-f® 75 IU（5.5 mcg）

本藥限由醫師使用

衛署菌疫輸字第000763號

成分

主成分：follitropin alfa

Follitropin alfa是利用中國倉鼠卵巢細胞（Chinese Hamster Ovary（CHO）Cell）經由基因工程製造而產生的濾泡刺激激素。

組成

每支含Follitropin alfa 5.5微克（75國際單位）。

每毫升含75國際單位。

臨床特性

適應症

女性患者

（1）婦女經Clomiphene Citrate治療，仍無法排卵者（含多囊性卵巢症，PCOD）。

（2）對於實施人工生殖協助技術（ART），如體外受精（IVF），配子輸卵管植入（GIFT），合子輸卵管植入（ZIFT）的患者，可刺激其多濾泡發育。

男性患者

GONAL-f®併用人類絨毛膜性腺刺激素（hCG），用於治療患有先天或後天性腺刺激素不足之性腺功能低下症之男性患者，以刺激精子生成。

用法用量

GONAL-f®應由對不孕症治療有經驗的醫師監督下使用。

建議劑量

GONAL-f®的建議劑量與目前使用的尿液製劑FSH相同。根據臨床分析顯示，不論在每日劑量、投與方式或治療監測過程，GONAL-f®與目前使用的尿液製劑FSH並無不同。建議劑量如下。

但在比較GONAL-f®與尿液製劑FSH的臨床試驗結果顯示使用GONAL-f®的患者平均可用較低的總劑量及較短的治療期間來達成療效。因此，GONAL-f®治療可比一般的尿液製劑FSH給予較低的總劑量，不僅是為了達到誘發濾泡發育的最佳化，也為了讓卵巢過度刺激的危險性減到最低。

無排卵症之女性患者（包括多囊性卵巢症候群）

GONAL-f®可以以每日注射的療程來進行。對於有月經之女性患者，應在月經週期的前七天內開始治療。

一般以每天注射75 IU至150 IU的FSH，每七或十四天為劑量調整時段，視情況增加37.5 IU或75 IU，以期產生足夠但不太過的反應。治療計劃須依患者本身的反應做一適當的調整，其評估測量包括（1）以超音波測量濾泡大小（2）動情激素的分泌。每日最大劑量通常不超過225 IU。若患者連續治療四星期後仍無反應，必須放棄此一療程。患者應先接受進一步的評估，然後再重新開始下一次治療，開始建議劑量應高於前次放棄療程所使用的開始建議劑量。

達最佳反應時，在注射最後一劑的GONAL-f®後24至48小時內，施以單一注射的250 mcg r-hCG或5,000~10,000 IU hCG。建議患者在注射絨毛膜性腺刺激素（hCG）當天及隔天同房，或是進行子宮內受精（IUI）。

若產生過度反應，則須中止治療且不得給予絨毛膜性腺刺激素（hCG）（請參考警語），並建議下次的治療週期，須調降治療劑量。

針對接受試管嬰兒或其他生殖技術的婦女

超排卵治療計劃自月經週期的第二或第三天開始，每天給予GONAL-f® 150-225 IU，持續治療至濾泡發育完成（以監測血中雌激素濃度和/或超音波檢查來偵測），並依患者的反應做劑量的調整，一般最高劑量每天不超過450 IU。通常完整的濾泡發育平均需要十天左右（5-20天之間）。

在注射最後一劑GONAL-f®後24至48小時內，施以單一注射的250 mcg r-hCG或5,000 ~ 10,000 IU hCG，以促進最後濾泡的成熟。

以性腺刺激素釋放激素類似物（GnRH agonist）或拮抗劑（antagonist）下降調節（down regulation）已普遍使用以達到抑制內生性黃體生成激素高峰（LH surge）的產生及控制黃體生成激素（LH）的濃度。一般常用的療程為先使用性腺刺激素釋放激素類似物（GnRH agonist）二週後，再開始使用GONAL-f®，兩者持續使用，直至產生滿意的成熟濾泡。例如：以性腺刺激素釋放激素類似物（GnRH agonist）連續治療二週後，再開始投予GONAL-f® 150~225 IU，連續注射七天，然後依卵巢的反應而調整劑量。

以目前IVF治療的經驗而言，通常在前四次治療的懷孕率將保持平穩，但之後懷孕率就會逐漸降低。

男性患者因性腺刺激激素分泌過低造成的性腺功能低下症

GONAL-f®的劑量應為150 IU每週投予三次，配合hCG治療至少四個月。若患者使用四個月後仍無反應，可以繼續合併治療。現有臨床經驗顯示，可能需要治療至少18個月以達到精子生成的效果。

用法

GONAL-f®以皮下注射給予。應每天更換注射部位。

患者自行注射GONAL-f®應有足夠意願、接受適當訓練且有管道可獲得專業建議。如果您自行施打GONAL-f®，需詳讀使用指南。

- GONAL-f®調配後需立即使用。
- 初次注射GONAL-f®應在醫師或護士的監督下進行。
- 醫師或護士應教導患者如何使用GONAL-f®來自我注射。

禁忌症

- 對follitropin alfa, FSH或其他賦形劑過敏者（參見“賦形劑”）
- 下視丘或腦下垂體腫瘤
- 非因多囊性卵巢症候群引起之卵巢增大或卵巢囊腫者
- 原因不明的陰道出血（病因不明之婦科出血）
- 卵巢、子宮或乳房的癌症

下列患者無法以GONAL-f®治療得到預期療效時，請勿使用。例如：

- 原發性卵巢衰竭之患者
- 生殖器官畸形而致無法懷孕者
- 子宮纖維瘤而致無法懷孕者
- 原發性睪丸功能不全之患者

若有上述情況之一者，請勿使用GONAL-f®。若無法確定，請於使用本藥品之前先諮詢醫師或藥師。

警語與注意事項

GONAL-f®是一強效的性腺刺激素，可能會引起輕到嚴重的副作用，必須由對不孕症問題與處理完全了解的醫師使用。性腺刺激素的治療需要專業醫師在適當的監測設備下治療一段時間。

婦女要安全有效的使用GONAL-f®，必須用超音波定期掃描卵巢的反應或同時測量血中oestradiol的濃度。患者對FSH的反應可能各不相同。不論男女患者採用最低的有效劑量為治療原則。

紫質症

若您或任何家族成員罹患紫質症（一種無法分解紫質的疾病，可能由父母遺傳給子女），在開始治療前請告知您的醫師，因為GONAL-f®可能會增加紫質症急性發作的危險性。罹患紫質症或有紫質症家族病史之患者在接受GONAL-f®治療期間應特別小心監測。若發生紫質症惡化或出現紫質症病徵，患者可能需要停止治療。

若有下列情況，請立即告知醫師：

- 皮膚變得脆弱且容易起水泡，尤其是經常暴露於陽光下的皮膚，和/或
- 發生胃痛、手臂或腿部疼痛。若有上述情況，醫師可能會建議停止治療。

治療女性患者

在以GONAL-f®治療之前，不孕的夫婦應先有適切的診斷。GONAL-f®並不建議用於無法獲得預期療效的情況，例如原發性卵巢功能衰竭、導致不孕的性器官畸形或通常認為會導致不孕的子宮纖維腫瘤。特別需評估患者是否有甲狀腺功能不足、腎上腺皮質功能不全、泌乳激素過高，並給予適當的治療。

患者不管是因無排卵不孕症或用人工協助生殖技術治療而進行超排卵時，有可能會導致卵巢腫大或卵巢的過度刺激，但只要遵守GONAL-f®的使用劑量與療程並小心監測，就可降低這些現象。濾泡的發展與成熟度需要靠有經驗的醫師的敏銳解析。

臨床試驗顯示當使用lutropin alfa時會增加GONAL-f®對卵巢的敏感度。當需要增加FSH的劑量時，最好每7-14天調整劑量且調整劑量在37.5-75 IU之間。無GONAL-f®/LH與促性腺激素（hMG）的直接比較報告。比較過去數據顯示用GONAL-f®/LH與hMG的排卵率是相似的。

卵巢過度刺激症候群(Ovarian Hyperstimulation Syndrome, OHSS)

使用本藥品會增加OHSS發生的危險性，這是當濾泡數目產生過多並變成大的囊腫。若確實遵循建議使用劑量及時程，發生OHSS的可能性較低。

若發生下腹疼痛、體重快速增加、噁心、嘔吐或呼吸困難，應立即告知醫師，醫師可能會要求停止使用本藥（參見“不良反應”）。

使用GONAL-f®治療很少引起嚴重OHSS，除非投與用來促使最後濾泡成熟的藥物（含hCG）。若發生OHSS，醫師在這個治療週期內可能不會給予任何hCG，而且可能會建議至少四天內不能有性行為或應採用保險套等隔絕式避孕法（barrier contraceptive methods）。

某種程度的卵巢增大是控制性卵巢刺激可以預期的效果，較常見於多囊性卵巢症候群的女性患者，通常無需治療就會消退。

不同於單純性卵巢增大，OHSS會隨著嚴重度增加而症狀更顯著，包括明顯的卵巢增大、高濃度之血中性類固醇以及增加血管的滲透性而導致腹膜、胸膜及罕見的心包膜腔的體液聚積。

輕度的OHSS症狀包括腹痛、腹部不適、腹脹及卵巢增大。中度的OHSS症狀可能還會出現噁心、嘔吐、超音波可見的腹水及明顯的卵巢增大。

嚴重的OHSS症狀包括腹痛、腹脹、嚴重的卵巢增大、體重增加、呼吸困難、尿量減少與腸胃道症狀包括噁心、嘔吐與腹瀉。臨床上可能出現血容積過少、血液濃度增加、電解質不平衡、腹水、腹膜積血、肋膜腔積水或急性肺窘迫的現象。嚴重的OHSS也可能併發罕見的卵巢扭轉或血栓栓塞狀況如肺栓塞、缺血性中風及心肌梗塞。

引發OHSS的危險因子包括年紀輕、體質瘦弱、多囊性卵巢症候群、使用較高劑量之外生性性腺刺激素、血清雌激素（oestradiol）濃度高或快速上升（如在無排卵症患者中，血中oestradiol濃度高於900 pg/mL或3300 pmol/L；在ART患者中，血中oestradiol濃度高於3000 pg/mL或11000 pmol/L），以及曾經發生過OHSS、大量正在發育的卵巢濾泡（如在無排卵患者中，濾泡直徑≥14 mm數目有3個以上時；在ART患者中濾泡直徑≥ 12 mm數目有20個以上時）。

確實遵循GONAL-f®的建議投予劑量及方式能降低卵巢過度刺激的危險性，建議利用超音波掃描及測量雌激素來監測刺激週期以利早期發現危險因子。

證據顯示hCG是誘發OHSS的一個主要關鍵，此症候群還可能因懷孕而更嚴重且拖延更久。若發生卵巢過度刺激的徵兆，如血中oestradiol高於5500 pg/mL或20200 pmol/L及/或總濾泡數≥ 40個，建議停止使用hCG治療，並建議患者停止性行為或使用保險套等隔絕式避孕法至少四天。OHSS可能進展快速（24小時之內）或在幾天內變嚴重，通常出現在停用荷爾蒙後約7-10天後最嚴重，故患者在給予hCG後應繼續追蹤至少兩週。

人工協助生殖技術，在自發性排卵前吸出所有的濾泡可降低過度刺激的發生率。輕度或中度的OHSS通常會自然消退。若發生嚴重的OHSS，建議將進行中的性腺刺激素療程停止，患者應住院接受適當的治療。

多胞胎懷孕

使用GONAL-f®的患者其發生多胞胎懷孕（大部分是雙胞胎）的危險性較自然受孕者高。多胞胎懷孕對母體及嬰兒均有較高風險。

為減少多胞胎懷孕的危險性，建議醫師應小心監測卵巢的反應。

人工協助生殖技術產生多胞胎懷孕的危險性主要與患者年齡、植入受精卵或胚胎的個數及品質有關。

在治療前應告知患者有多胞胎的潛在風險。

懷孕流產

進行人工協助生殖技術或刺激卵巢以製造卵子（濾泡發育）較一般婦女更容易發生流產。

子宮外孕

不管是自然懷孕或接受不孕症治療，只要婦女有輸卵管疾病史，就有子宮外孕的風險。接受人工協助生殖技術後的子宮外孕發生率較一般人高。

生殖系統腫瘤

曾有婦女在接受多種不孕症治療後，發生良性與惡性卵巢和其它生殖系統腫瘤的報導。但尚未證實性腺刺激素是否會增加不孕婦女罹患腫瘤的危險性。

先天性畸形

人工協助生殖技術所伴隨的先天性畸形（出生缺陷）發生率可能略高於自然受孕者。可能是由於父母的因素（例如母親的年齡，精子的特徵）、人工協助生殖技術步驟及多胞胎。

血管栓塞

近期曾經或正罹患血管栓塞疾病（腿或肺內血栓、或心臟病發作或中風）的婦女，或有血管栓塞發生的潛在風險如個人或家族病史的婦女，使用性腺刺激素治療可能更增加血栓栓塞惡化或發生的危險性。對這些婦女須仔細衡量給予性腺刺激素的效益與風險。同時應注意懷孕本身以及OHSS也會增加血栓栓塞的風險。

治療男性患者

為了監測療效，醫師可能會在開始治療4-6個月後請患者提供精液進行分析。

治療前內生性FSH濃度上升表示原發性睪丸衰竭，這類患者對GONAL-f®/hCG治療沒有反應，當預期無法獲得有效反應時，不應使用GONAL-f®。

納含量

GONAL-f®每一劑量含納少於1 mmol（23 mg），基本上為不含納。

交互作用

若您正在使用或近期曾經使用其他藥物包括或非處方藥物，請告知醫師或藥師。

GONAL-f®與其他刺激排卵的藥物（如hCG、clomiphene citrate）併用會加強濾泡反應，而與性腺刺激素釋放激素類似物（GnRH agonist）或拮抗劑（GnRH antagonist）併用以促使腦下垂體作用失去敏感度，則可能需增加GONAL-f®誘發適當卵巢反應所需的使用劑量。

懷孕與授乳

懷孕

懷孕期間不適用。

有限的相關懷孕案例數據顯示（少於300個懷孕案例），follitropin alfa沒有畸胎或胎兒/新生兒毒性。

動物試驗並未發現致畸胎作用，但臨床數據仍不足以排除懷孕期間暴露於GONAL-f®而造成致畸胎作用的可能性。

授乳

GONAL-f®不適合授乳期間使用。在授乳期間，prolactin的分泌會對刺激排卵產生不良預後。

不良反應

安全性概述

最常見的不良反應為頭痛、卵巢囊腫及注射部位之局部反應（如：痛、紅、血腫或刺激感等）。輕至中度的卵巢過度刺激症候群（OHSS）常見，但嚴重的OHSS則不常見。

下列定義為發生頻率專用詞適用於後續敘述：

- 十分常見（> 1/10）
- 常見（> 1/100, < 1/10）
- 不常見（> 1/1,000, < 1/100）
- 罕見（> 1/10,000, < 1/1,000）
- 非常罕見（< 1/10,000）

女性患者的不良反應

免疫系統疾病

非常罕見：輕至重度的過敏反應，包括全身過敏性反應和休克。

神經系統疾病

十分常見：頭痛。

血管疾病

罕見：血栓栓塞。

呼吸、胸腔及縱膈疾病

非常罕見：氣喘惡化。

消化道疾病

常見：腹痛、腫脹、腹部不適、噁心、嘔吐、腹瀉。

生殖系統及乳房疾病

十分常見：卵巢囊腫。

常見：輕至中度OHSS及相關症狀。

不常見：嚴重的OHSS及相關症狀。

罕見：嚴重OHSS之併發症。

一般性疾病及注射部位症狀

十分常見：注射部位的局部反應（如：痛、紅、血腫、腫脹或刺激感）。

男性患者的不良反應

免疫系統疾病

非常罕見：輕至重度的過敏反應，包括全身過敏反應和休克。

呼吸、胸腔和縱膈疾病

非常罕見：氣喘惡化。

皮膚及皮下組織疾病

常見：痤瘡。

生殖系統及乳房疾病

常見：男性女乳症，精索靜脈曲張。

一般性疾病及注射部位症狀

十分常見：注射部位的局部反應（如：痛、紅、血腫、腫脹或刺激感）。

檢查

常見：體重增加。

過量

過量GONAL-f®產生的反應在男性尚未知曉，但在女性有可能發生OHSS，請參見警語與注意事項。

藥理特性

GONAL-f®所含的藥物為follitropin alfa。Follitropin alpha是一種屬於性腺刺激素（Gonadotropins）的濾泡刺激激素（Follicle Stimulating Hormone, FSH），性腺刺激素的作用與生殖和受孕有關。

藥效學

藥理分類：性腺刺激素

ATC code: G03GA05

在女性，以非經腸道方式投予濾泡刺激激素，最主要的效用是促進成熟濾泡的產生。

對於無法排卵的婦女，GONAL-f®的治療目標是產生單一成熟的卵巢濾泡（Graafian follicle），然後經由投與人類絨毛膜性腺刺激素（hCG）後促進排卵。

女性臨床療效與安全性

在臨床試驗，於中央實驗室測量血中LH濃度< 1.2 IU/l則定義為嚴重的FSH與LH不足。但須考慮在不同的實驗室對LH的測量會有不同。

在比較經由基因工程製造之r-hFSH和尿液製劑FSH用於人工協助生殖技術（assisted reproductive technologies, ART）及誘發排卵的臨床試驗中發現，GONAL-f®比尿液製劑FSH可以用較低的總劑量及較短的治療期間來達到誘發濾泡成熟的療效。進行ART時，GONAL-f®顯示可以使用比尿液製劑FSH較低的總劑量及較短的治療期間，結果所取得的卵母細胞數量也較尿液製劑FSH為多。

表：GF8407試驗結果（比較GONAL-f®和尿液製劑FSH用於人工生殖協助技術之療效與安全性之隨機平行性試驗）

	GONAL-f®（n=130）	尿液製劑FSH（n=116）
取得的卵母細胞數量	11.0 ± 5.9	8.8 ± 4.8
所需的FSH刺激天數	11.7 ± 1.9	14.5 ± 3.3
所需的FSH總劑量（FSH 75 IU安瓿的數量）	27.6 ± 10.2	40.7 ± 13.6
需要增加劑量（%）	56.2	85.3

** 兩組之間所有評估條件比較結果均顯示有統計上的顯著差異（$p < 0.05$）。*

男性臨床療效與安全性

缺乏FSH之男性，GONAL-f®與hCG併用治療至少四個月可以誘導精子生成。

藥物動力學

GONAL-f®的藥物動力學特性基本上與人類的FSH的藥物動力學特性相似。

吸收：皮下注射投與後，絕對的生物可用率大約為70%，若重覆投予，在3-4天內follitropin alfa於穩定狀態下累積量達3倍。

分佈：靜脈注射投與後，follitropin alfa分佈於細胞外液體腔，起始的半衰期約為2小時；由體內排除時，最終半衰期大約1天。達穩定狀態的分佈體積與總清除率各為10 L及0.6 L/h。

排除：1/8的follitropin alfa由尿液排泄。

非臨床的安全性資料

依據單一、重複劑量毒性及基因毒性的傳統文獻之非臨床資料顯示本品對人類並無已在仿單的其他段落中有敘述以外的特定危害。

由於基因工程製造之FSH（r-hFSH）與人類的FSH基本上是相似的，故並未針對follitropin alfa進行有關致癌性的活體試驗，使用GONAL-f®治療預期並無致癌性危險。

當老鼠長期投與follitropin alfa ≥ 40 IU/公斤/天的劑量，生產數目會降低。

與尿液hMG製劑相同，當投與高劑量的follitropin alfa（≥ 5 IU/公斤/天）後，會造成能存活的胚胎數減少，但不會造成畸形或難產。由於孕婦不能使用GONAL-f®，所以這方面的臨床資料有限。

藥劑學特性

賦形劑：sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, methionine, polysorbate 20, concentrated phosphoric acid and sodium hydroxide.

溶劑：Water for injections.

不相容性

除了lutropin alfa或經由研究顯示其合併投予並未造成主成分的活性、安定性、藥物動力學特性及藥效學特性顯著改變之lutropin alfa加follitropin alfa組合外，GONAL-f®不能與其它藥品同時混合注射。

GONAL-f®能與lutropin alfa一起調配注射，應先溶解lutropin alfa後再以此溶液調配GONAL-f®粉末。

儲存注意事項

藥品須於25℃以下貯存。藥品須放在原包裝以避光貯存。

若發現GONAL-f®有可見的變質跡象，及藥物溶液含顆粒或非澄清液體則不可使用。

請勿使用已過有效期限的藥品。

請放置在孩童取得不到的地方。

包裝

GONAL-f® 75國際單位（5.5微克）一支小瓶裝，附等支數1公撮注射針筒裝溶劑（附注射針）。

使用說明

這個章節將告訴您如何準備及使用GONAL-f®藥品。

開始準備前請先詳閱整份說明。

應在每日的同一時間進行自我注射。

1. 洗手及選擇乾淨的區域

- 您的手及所使用的器具須盡可能的乾淨，這是很重要的。
- 好的地方是指乾淨的桌子或廚房桌面。

2. 準備所需要的物品及陳列出所有的東西：

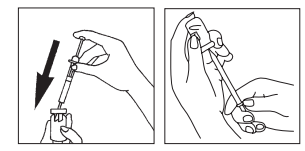
- 一支稀釋溶劑（澄清液體）
- 一瓶藥品（白色粉末）
- 一支溶解用的針頭
- 一支皮下注射用針頭

包裝內未附物品

- 兩個酒精棉球
- 一個容器

3. 準備注射液

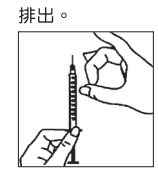
- 打開藥品及溶劑針筒的蓋子。
- 將溶解用的針頭裝到溶劑針筒上，小心地將針筒內溶劑慢慢注入含GONAL-f®的小瓶中。針筒不必拔出並輕輕旋轉藥瓶。不可用力搖晃。
- 檢查溶液是否為澄清無顆粒的。
- 將藥品反轉，並將稀釋好的藥液透過反抽慢慢吸至針筒。
- 將針筒從小瓶上移除並小心放下。不要觸碰針頭及不可讓針頭碰觸到其它地方。



（如果處方超過一瓶以上的GONAL-f®，則將稀釋好的藥液慢慢吸回針筒，再注入其它欲稀釋的粉末中。如果您必須同時使用lutropin alfa，您可將這兩種藥品一起溶解注射。先溶解lutropin alfa後再將溶液注入含GONAL-f®的瓶中。溶解後將藥液抽回注射筒中並檢查溶液是否為澄清無顆粒的。一毫升的稀釋液最多可溶三瓶藥品。）

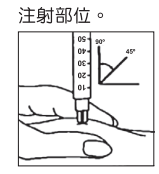
4. 準備好注射針筒

- 更換注射用的針頭。
- 除去氣泡：如果看見針筒裡有氣泡，將針頭向上並輕彈針筒直到氣泡集中於針筒上端，推針筒活塞使氣泡完全排出。



5. 注射劑量

- 馬上注射藥品：醫師或護士建議之注射部位（肚子、大腿正面），為降低對皮膚的刺激，每天應選擇不同的注射部位。
- 先以酒精棉球用畫圓的方式消毒注射部位。
- 捏緊皮膚，針頭以45°-90°角注射於皮膚下。
- 不可直接注射到血管，依照指示方式注射到皮下並慢慢推針筒活塞，直到注射完藥液。
- 注射完後立刻拔出針頭並以酒精棉球用畫圓的方式清潔注射部位。



6. 注射完畢

- 丟棄所有使用過的器具：每次注射完畢，丟棄所有的針頭與空的玻璃容器於特定容器中。任何未使用完的溶液均須丟棄。

資料日期

2017年1月

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