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Merck Serono

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GONAL-f® 300 IU/450 IU/900 IU

solution for injection in pre-filled pen

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

GONAL-f 300 IU solution for injection in pre-filled pen:

Each ml of the solution contains 600 IU (International Units) of follitropin alfa, (equivalent to 44 micrograms). Each pre-filled multidose pen delivers 300 IU (equivalent to 22 micrograms) in 0.5 ml.

GONAL-f 450 IU solution for injection in pre-filled pen:

Each ml of the solution contains 600 IU (International Units) of follitropin alfa, (equivalent to 44 micrograms). Each pre-filled multidose pen delivers 450 IU (equivalent to 33 micrograms) in 0.75 ml.

GONAL-f 900 IU solution for injection in pre-filled pen:

Each ml of the solution contains 600 IU (International Units) of follitropin alfa, (equivalent to 44 micrograms). Each pre-filled multidose pen delivers 900 IU (equivalent to 66 micrograms) in 1.5 ml.Excipients: poloxamer 188, sucrose, methionine, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, m-cresol, concentrated phosphoric acid, sodium hydroxide and water for injections.

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

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).

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.

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.

Indications

Women

Anovulation including polycystic ovarian syndrome in women who have been unresponsive to treatment with clomiphene citrate (helping release an egg from the ovary in women that cannot ovulate).

Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer (helping develop several follicles in women undergoing procedures that may help to become pregnant).

GONAL-f in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency (helping release egg from the ovary in women that are not ovulating because their body is producing very little gonadotropins). In clinical trials these patients were defined by an endogenous serum LH level < 1.2 IU/l.

Men

Stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy (helping produce sperm in men that are infertile due to a low level of certain hormones).

Contraindications

- Allergy (hypersensitivity) to the active ingredient follitropin alfa, FSH or to any of the excipients (see section 'Composition' 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 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

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.

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 severe ovarian enlargement, weight gain, dyspnoea or oliguria. Clinical evaluation may reveal signs such as hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, pleural effusions, or acute pulmonary distress. Very 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, higher doses of exogenous gonadotropins, high absolute or rapidly rising serum oestradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in ART cycles.

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, 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, 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.

You can reduce the risk of multiple pregnancy by using the right dose of GONAL-f at the right times. Careful monitoring of ovarian response by your doctor 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.

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.

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.

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.

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, genetics), ART procedures and multiple pregnancies.

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.

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 prior to treatment can be a sign of damaged testicles (primary testicular failure). Such patients are unresponsive to GONAL-f/hCG therapy.

Pregnancy and lactation

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.

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

Adverse reactions

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)

Serious adverse reactions in women

- Lower abdominal pain together with nausea or vomiting may be the symptoms of Ovarian Hyper-Stimulation Syndrome (mild or moderate OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed (see also section 'Special warnings and precautions' above). This adverse reaction is common.
- The OHSS may become severe with clearly enlarged ovaries, decreased urine production, weight gain, difficulty in breathing and/or possible fluid accumulation in your stomach or chest. This adverse reaction is uncommon.
- Complications of severe OHSS such as twisting of ovaries or blood clotting may occur rarely.
- Serious blood clotting complications (thromboembolic events) independent of OHSS may be found very rarely. This could cause chest pain, breathlessness, stroke or heart attack (see also section 'Special warnings and precautions' above).

To prevent serious adverse reactions, speak to a doctor immediately if you experience any of these symptoms.

Serious adverse reactions in men and women

- Allergic reactions such as rash, red skin, hives or swelling of your face with difficulty breathing can sometimes be serious (mild to severe hypersensitivity reactions including anaphylactic reactions and shock). This adverse reaction is very rare.

To prevent serious adverse reactions, speak to a doctor immediately if you experience any of these symptoms.

Other adverse reactions in women

Very common

- Sacs of fluid within the ovaries (ovarian cysts)
- Headache
- Local reactions at the injection site, such as pain, redness, bruising, swelling or irritation

Common

- Feeling sick, vomiting, diarrhoea, abdominal pain or cramps, bloating

Very rare

- Worsening of asthma

Other adverse reactions in men

Very common

- Local reactions at the injection site, such as pain, redness, bruising, swelling and/or irritation

Common

- Swelling of the veins above and behind the testicles (varicocele)
- Breast development (gynaecomastia), acne, weight gain

Very rare

- Worsening of asthma

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.

Dosage and administration

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

Your doctor will decide on the dose and schedule of administration, which are most appropriate for you during this course of treatment.

If you forget to use GONAL-f, do not take a double dose to make up for a forgotten dose. Please talk to your doctor as soon as you notice that you forgot a dose.

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 is usually given every day. In menstruating women treatment should commence within the first 7 days of the menstrual cycle otherwise treatment can be started on any convenient day.

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 the treatment may be recommenced 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 best time to have sex is on the day of the hCG injection and the day after. Alternatively intrauterine insemination (IUI) may be performed.

If an excessive response is obtained, treatment should be stopped and (r-)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 (development of several eggs for collection prior to any ART) 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 (when the eggs are ready), with the dose adjusted according to the patient's response, to usually not higher than 450 IU daily. This usually takes about 10 days but can take any time between 5 and 20 days and is assessed by monitoring of serum oestrogen concentrations and/or ultrasound examination.

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 (get the eggs ready for collection).

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 (you may first be stopped from ovulating). 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. When GnRH antagonist is used, it is administered from the 5th or 6th day of GONAL-f treatment and continued until ovulation induction.

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

Women with anovulation resulting from severe LH and FSH deficiency

In LH and FSH deficient women (hypogonadotrophic hypogonadism), the objective of GONAL-f therapy in association with lutropin alfa is to develop a single mature Graafian follicle from which the oocyte will be liberated after the administration of hCG. GONAL-f should be given as a course of daily injections simultaneously with lutropin alfa. Since these patients are amenorrhoeic and have low endogenous oestrogen secretion, treatment can commence at any time.

Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response. The usual starting dose of GONAL-f is 75 - 150 IU together with 75 IU of lutropin alfa.

These two medicines will be used each day for up to 5 weeks. If a response cannot be seen after 5 weeks, that treatment cycle with GONAL-f should be stopped. For the following cycle, the dose of GONAL-f may be increased every 7 or every 14 days by 37.5 - 75 IU, until the desired response is obtained.

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 and lutropin alfa injections. The best time to have sex is on the day of the hCG injection and the day after. Alternatively intrauterine insemination (IUI) may be performed by placing the sperm into the womb cavity.

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

Luteal phase support may be considered since lack of hormones with luteotrophic activity (LH/hCG) after ovulation may lead to premature failure of the corpus luteum.

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 (injection just under the skin). 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 in the pack.

- The pre-filled pen can be used for several injections.
- The first injection of GONAL-f should be given under supervision of your doctor.
- Your doctor or nurse will show you how to use the GONAL-f pre-filled pen to inject the medicine.

As GONAL-f pre-filled pen with multidose cartridge is intended for several injections, clear instructions should be provided to the patients to avoid misuse of the multidose presentation.

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. However this will only occur if hCG is administered.

Storage and stability

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package, in order to protect from light.

Before opening and within its shelf life, the pre-filled pen may be removed from the refrigerator, without being refrigerated again, for up to 3 months at or below 25°C. The product must be discarded if it has not been used after 3 months.

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

Write on the GONAL-f pre-filled pen the day you first use it.

- Once opened, it may be stored for a maximum of 28 days outside of the fridge (at or below 25°C).
- Do not use any medicine left in your pre-filled pen after 28 days. At the end of the treatment any unused solution must be discarded.

Do not use after the expiry date.

Keep medicines out of the reach of children.

Presentations

GONAL-f 300 IU solution for injection in pre-filled pen:

Pack of 1 pre-filled pen and 8 needles to be used with the pen for administration.

GONAL-f 450 IU solution for injection in pre-filled pen:

Pack of 1 pre-filled pen and 12 needles to be used with the pen for administration.

GONAL-f 900 IU solution for injection in pre-filled pen:

Pack of 1 pre-filled pen and 20 needles to be used with the pen for administration.

Not all presentations may be registered or marketed.

Manufacturer:

Merck Serono S.p.A.
Via delle Magnolie 15 (loc. frazione Zona Industriale)
70026 - Modugno (BA) - Italy

Marketing Authorization Holder in Europe:

Merck Serono Europe Limited
E 14 9 TP, London
United Kingdom

Date of information

June 2011

This is a Medicine

Medicine is a product, which affects your health and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicine.

- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- **Keep all medicines away of reach of children.**

Council of Arab Health Ministers
& Union of Arab Pharmacists.