1. NAME OF THE MEDICINAL PRODUCT

GONAL-f™ 75 IU (5.5 micrograms), powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 5.5 micrograms of follitropin alfa* equivalent to 75 IU. Each ml of the reconstituted solution contains 75 IU.
* recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Appearance of the powder: white lyophilised pellet.
Appearance of the solvent: clear colourless solution.
The pH of the reconstituted solution is 6.5-7.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adult 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 and zygote intra-fallopian transfer.

4.2 Posology and method of 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. See section 5.1.

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 recommence 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 (f-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 may be performed.

If an excessive response is obtained, treatment should be stopped and hCG withheld (see section 4.4). Treatment should recommence in the next cycle at a dose 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 concentrations 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 recombinant human choriogonadotropin alfa (f-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 IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

Special population

Elderly population

There is no relevant use of GONAL-f™ in the elderly population. Safety and effectiveness of GONAL-f™ in elderly patients have not been established.

Renal or hepatic impairment

Safety, efficacy and pharmacokinetics of GONAL-f™ in patients with renal or hepatic impairment have not been established.

Paediatric population

There is no relevant use of GONAL-f™ in the paediatric population.

Method of administration

GONAL-f™ is intended for subcutaneous administration. The first injection of GONAL-f™ should be performed under direct medical supervision. 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. For instructions on the reconstitution and administration of GONAL-f™ powder and solvent for solution for injection, see section 6.6.

4.3 Contraindications

- hypersensitivity to the active substance follitropin alfa, FSH or to any of the excipients
- tumours of the hypothalamus or pituitary gland

In women:

- ovarian enlargement or ovarian cyst not due to polycystic ovarian disease
- gynaecological haemorrhages of unknown aetiology
- ovarian, uterine or mammary carcinoma

GONAL-f™ must not be used when an effective response cannot be obtained, such as:
In women:

- primary ovarian failure
- malformations of sexual organs incompatible with pregnancy
- fibroid tumours of the uterus incompatible with pregnancy

4.4 Special warnings and special precautions for use

GONAL-f™ is a potent gonadotrophic 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.

Porphyria
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.

Treatment in women
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 appropriate specific treatment given.

Patients undergoing stimulation of follicular growth, whether in the frame of treatment for anovulatory infertility or 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 the relevant tests.

In clinical trials, an increase of the ovarian sensitivity to GONAL-f™ was shown when administered with lutropin alfa. If an FSH dose increase is deemed appropriate, dose adaptation 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 data suggests that the ovulation rate obtained with GONAL-f /LH is similar to that obtained with hMG.

Ovarian Hyperstimulation Syndrome (OHSS)

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.

The following symptomatology may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax oracute 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 polycystic ovarian syndrome 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 large number of developing ovarian follicles (e.g. > 3 follicles of ≥ 14 mm in diameter in anovulation; ≥ 20 follicles of ≥ 12 mm in diameter in ART) and large numbers of oocytes retrieved in ART cycles.

Adherence to recommended GONAL-f™ dosage and regimen of administration can minimise the risk of ovarian hyperstimulation (see sections 4.2 and 4.8). 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 to 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

In patients undergoing ovulation induction, the incidence of multiple pregnancy is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancy, especially of high order, carries an increased risk of adverse maternal and perinatal outcomes.

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

In patients undergoing ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient age.

The patients should be advised of the potential risk of multiple births before starting treatment.

Pregnancy loss

The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than following natural conception.

Ectopic pregnancy

Women with a history of tubal disease are at risk of ectopic pregnancy, 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 drug 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 malformation

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

Thromboembolic events

In women with recent or ongoing thromboembolic disease or women with generally recognised risk factors for thrombo-embolic 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 thrombo-embolic events.

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of GONAL-f™ with other medicinal products 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 dose of GONAL-f™ needed to elicit an adequate ovarian response. No other clinically significant medicinal product interaction has been reported during GONAL-f™ therapy.
GONAL-f™ should not be administered as mixture with other medicinal products, in the same injection, except lutropin alfa for which studies have shown that co-administration does not significantly alter the activity, stability, pharmacokinetic nor pharmacodynamic properties of the active substances.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no indication for use of GONAL-f™ during pregnancy. Data on a limited number of exposed pregnancies (less than 300 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of follitropin alfa. No teratogenic effect has been observed in animal studies (see section 5.3).
In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of GONAL-f™.

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

Fertility
GONAL-f™ is indicated for use in infertility (see section 4.1).

4.7 Effects on ability to drive and use machines

GONAL-f™ is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse reactions are headache, ovarian cysts and local injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection).

Mild or moderate ovarian hyperstimulation syndrome (OHSS) have been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

The following definitions apply to the frequency terminology used hereafter:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)

The following adverse reactions may be observed after administration of GONAL-f™

Treatment in women

Immune system disorders
Very rare: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Respiratory, thoracic and mediastinal disorders
Very rare: Exacerbation or aggravation of asthma

General disorders and administration site conditions
Very common: Injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

Nervous system disorders
Very common: Headache

Vascular disorders
Rare: Thromboembolism

Gastrointestinal disorders
Common: Abdominal pain, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhoea

Reproductive system and breast disorders
Very common: Ovarian cysts
Common: Mild or moderate OHSS (including associated symptomatology)
Uncommon: Severe OHSS (including associated symptomatology) (see section 4.4)

Rare: Complication of severe OHSS

4.9 Overdose

The effects of an overdose of GONAL-f™ are unknown. Nevertheless, there is a possibility that OHSS may occur (see section 4.4)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, 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 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 (follitropin alfa) and urinary FSH in ART (see table below) 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.

5.2 Pharmacokinetic properties

Following intravenous administration, GONAL-f™ 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. One-eighth of the GONAL-f™ dose is excreted in the urine.

Following subcutaneous administration, the absolute bioavailability is about 70 %. Following repeated administration, GONAL-f™ accumulates 3-fold achieving a steady state within 3-4 days. In women whose endogenous gonadotropin secretion is suppressed, follitropin alfa has nevertheless been shown to effectively stimulate follicular development and steroidogenesis, despite unmeasurable LH levels.

5.3 Preclinical safety data

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
Sodium dihydrogen phosphate monohydrate
Disodium phosphate dihydrate
Methionine
Polysorbate 20
Phosphoric acid, concentrated
Sodium hydroxide

Solvent
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Please refer to expiry date on outer carton.
For immediate and single use following first opening and reconstitution.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

GONAL-f™ is presented as a powder and solvent for injection. The powder is presented in 3 ml vials (Type I glass), with rubber stopper (bromobutyl rubber) and aluminium flipoff cap. The 1 ml solvent for reconstitution is presented in 1 ml pre-filled syringes (Type I glass) with a rubber stopper.
The medicinal product is supplied in packs of 1, 5, or 10 vials with 1, 5 or 10 of solvent pre-filled syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

GONAL-f™ must be reconstituted with the solvent before use (see section "How to prepare and use the GONAL-f™ powder and solvent" below).
GONAL-f™ may be co-reconstituted with lutropin alfa and coadministered as a single injection. In this case lutropin alfa should be reconstituted first and then used to reconstitute GONAL-f™ powder. Studies have shown that co-administration with lutropin alfa, does not significantly alter the activity, stability, pharmacokinetic nor pharmacodynamic properties of the active substances.
The reconstituted solution should not be administered if it contains particles or is not clear.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

IF YOU ADMINISTER GONAL-f™ TO YOURSELF, PLEASE CAREFULLY READ THE FOLLOWING INSTRUCTIONS:

HOW TO PREPARE AND USE THE GONAL-f™ POWDER AND SOLVENT

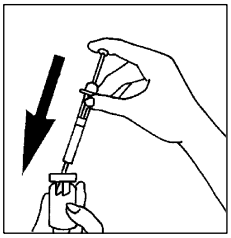
- This section tells you how to prepare and use your GONAL-f™ powder and solvent.
- Before starting the preparation, please read these instructions the whole way through first.
- Give yourself the injection at the same time each day.

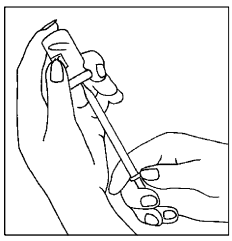
1. Wash your hands and find a clean area
- It is important that your hands and the items you use be as clean as possible.
- A good place is a clean table or kitchen surface.

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)

Not provided in the pack:
- 2 alcohol swabs
- 1 needle for preparation
- 1 fine bore needle for injection under the skin
- 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 (1 ml). Swirl gently without removing the syringe. Do not shake.
- After the powder has dissolved (which usually occurs immediately), 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.

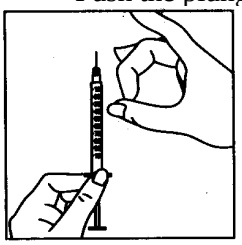




(If you have been prescribed more than one vial of GONAL-f™, slowly re inject the solution into another powder vial, until you have the prescribed number of powder vials dissolved in the solution. If you have been prescribed lutropin alfa in addition to GONAL-f™, you may also mix the two medicines as 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.)

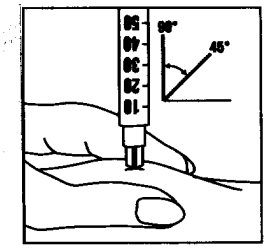
4. Getting ready the syringe for injection.

- 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.

Manufacturer
Merck Serono SA
Zone industrielle de l'Ouriettaz
CH-1170 Aubonne, Switzerland

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