

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GONAL-f 75 IU 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 the 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 to 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.
- GONAL-f in association with a luteinising hormone (LH) preparation is indicated for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men

- GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.

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 to 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 estrogen 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 (r-hCG) or 5 000 IU, up to 10 000 IU hCG should be administered 24 to 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 to 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 estrogen 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 r-hCG or 5 000 IU up to 10 000 IU hCG is administered 24 to 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 to 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.

Women with severe LH and FSH deficiency

In LH and FSH deficient women, the objective of GONAL-f therapy in association with a luteinising hormone (LH) preparation is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). GONAL-f should be given as a course of daily injections simultaneously with lutropin alfa. If the patient is amenorrhoeic and has low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75 to 150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and estrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7- to 14-day intervals and preferably by 37.5 to 75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.

When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG should be administered 24 to 48 hours after the last GONAL-f and lutropin alfa injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Men with hypogonadotropic hypogonadism

GONAL-f should be given at a dose of 150 IU three times a week, concomitantly 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.

Special populations

Elderly

There is no relevant use of GONAL-f in the elderly population. Safety and efficacy 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 use. The injection should be given at the same time each day.

The first injection of GONAL-f should be performed under direct medical supervision. Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

The injection site should be alternated daily.

For instructions on reconstitution of the medicinal product see section 6.6 and the package leaflet.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- tumours of the hypothalamus or pituitary gland
- ovarian enlargement or ovarian cyst unrelated to polycystic ovarian disease and of unknown origin

- gynaecological haemorrhages of unknown origin
- ovarian, uterine or mammary carcinoma

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 care 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 estradiol levels, on a regular basis. There may be a degree of inter-patient 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

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 as 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- to 14-day intervals and preferably with 37.5 to 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, 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 estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

Adherence to recommended GONAL-f dose 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 estradiol 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 estradiol level $> 5\,500\text{ pg/mL}$ or $> 20\,200\text{ pmol/L}$ 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. 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 reaches its maximum at about seven to ten 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

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 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 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 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

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.

Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response.

Sodium content

GONAL-f contains less than 1 mmol sodium (23 mg) per dose, i.e. it is 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.

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.

Breast-feeding

GONAL-f is not indicated during breast-feeding.

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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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) has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

Thromboembolism may occur very rarely (see section 4.4).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), very rare ($< 1/10\ 000$).

Treatment in women

Immune system disorders

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

Nervous system disorders

Very common: Headache

Vascular disorders

Very rare: Thromboembolism (both in association with and separate from OHSS)

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

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

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)
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Treatment in men

Immune system disorders

Very rare:	Mild to severe hypersensitivity reactions including anaphylactic reactions and shock
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Respiratory, thoracic and mediastinal disorders

Very rare:	Exacerbation or aggravation of asthma
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Skin and subcutaneous tissue disorders

Common:	Acne
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Reproductive system and breast disorders

Common:	Gynaecomastia, varicocele
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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)
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Investigations

Common:	Weight gain
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Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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 systems, gonadotropins, ATC code: G03GA05.

Mechanism of action

Follicle stimulating hormone (FSH) and luteinising hormone (LH) are secreted from the anterior pituitary gland in response to GnRH and play a complementary role in follicle development and ovulation. FSH stimulates the development of ovarian follicles, while LH action is involved in follicle development, steroidogenesis and maturation.

Pharmacodynamic effects

Inhibin and estradiol (E2) levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while E2 levels take more time, and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after 4 to 5 days of r-hFSH daily dosing, and, depending on patient response, the maximum effect is reached after about 10 days from the start of r-hFSH administration.

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.

Clinical efficacy and safety in men

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

5.2 Pharmacokinetic properties

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% of the follitropin alfa dose is excreted in the urine.

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 SmPC.

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 (for pH adjustment)
Sodium hydroxide (for pH adjustment)

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

3 years.

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 flip-off 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” in the package leaflet).

GONAL-f may be co-reconstituted with lutropin alfa and co-administered 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.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBERS

EU/1/95/001/025
EU/1/95/001/026
EU/1/95/001/027

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 1995.

Date of latest renewal: 20 October 2010.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

GONAL-f 1050 IU/1.75 mL powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each multidose vial contains 87 micrograms of follitropin alfa* (equivalent to 1 200 IU), in order to deliver 77 micrograms (equivalent to 1 050 IU) in 1.75 mL. Each mL of the reconstituted solution contains 600 IU.

* recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

Excipient with known effect: The reconstituted solution contains 9.45 mg benzyl alcohol per mL.

For the 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 to 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.
- GONAL-f in association with a luteinising hormone (LH) preparation is indicated for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men

- GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.

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.

Bioequivalence has been demonstrated between equivalent doses of the monodose presentation and the multidose presentation of GONAL-f.

The following table states the volume to be administered to deliver the prescribed dose:

Dose (IU)	Volume to be injected (mL)
75	0.13
150	0.25
225	0.38
300	0.50
375	0.63
450	0.75

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 to 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 estrogen 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 (r-hCG) or 5 000 IU, up to 10 000 IU hCG should be administered 24 to 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 to 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 estrogen 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 r-hCG or 5 000 IU up to 10 000 IU hCG is administered 24 to 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 to 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.

Women with severe LH and FSH deficiency

In LH and FSH deficient women, the objective of GONAL-f therapy in association with a luteinising hormone (LH) preparation is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). GONAL-f should be given as a course of daily injections simultaneously with lutropin alfa. If the patient is amenorrhoeic and has low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75 to 150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and estrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7- to 14-day intervals and preferably by 37.5 to 75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.

When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG should be administered 24 to 48 hours after the last GONAL-f and lutropin alfa injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Men with hypogonadotropic hypogonadism

GONAL-f should be given at a dose of 150 IU three times a week, concomitantly 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.

Special populations

Elderly

There is no relevant use of GONAL-f in the elderly population. Safety and efficacy 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 use. The injection should be given at the same time each day.

The first injection of GONAL-f should be performed under direct medical supervision. Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

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

Due to a local reactivity to benzyl alcohol, the same site of injection should not be used on consecutive days.

Individual reconstituted vials should be for single patient use only.

For instructions on reconstitution of the medicinal product see section 6.6 and the package leaflet.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- tumours of the hypothalamus or pituitary gland
- ovarian enlargement or ovarian cyst unrelated to polycystic ovarian disease and of unknown origin
- gynaecological haemorrhages of unknown origin
- ovarian, uterine or mammary carcinoma

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 care 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 estradiol levels, on a regular basis. There may be a degree of inter-patient 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

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 as 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- to 14-day intervals and preferably with 37.5 to 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, 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 estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

Adherence to recommended GONAL-f dose 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 estradiol 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 estradiol 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. 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 reaches its maximum at about seven to ten 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

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 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 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 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

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.

Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response.

Sodium content

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

Solvent containing benzyl alcohol

Following reconstitution with the solvent provided, this medicinal product contains 1.23 mg benzyl alcohol in each 75 IU dose, which is equivalent to 9.45 mg/mL. Benzyl alcohol may cause allergic reactions.

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.

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.

Breast-feeding

GONAL-f is not indicated during breast-feeding.

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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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) has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

Thromboembolism may occur very rarely (see section 4.4).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$), very rare ($< 1/10\,000$).

Treatment in women

Immune system disorders

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

Nervous system disorders

Very common: Headache

Vascular disorders

Very rare: Thromboembolism (both in association with and separate from OHSS)

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

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

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)

Treatment in men

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

Skin and subcutaneous tissue disorders

Common: Acne

Reproductive system and breast disorders

Common: Gynaecomastia, varicocele

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)

Investigations

Common: Weight gain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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 systems, gonadotropins, ATC code: G03GA05.

Mechanism of action

Follicle stimulating hormone (FSH) and luteinising hormone (LH) are secreted from the anterior pituitary gland in response to GnRH and play a complementary role in follicle development and ovulation. FSH stimulates the development of ovarian follicles, while LH action is involved in follicle development, steroidogenesis and maturation.

Pharmacodynamic effects

Inhibin and estradiol (E2) levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while E2 levels take more time, and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after 4 to 5 days of r-hFSH daily dosing, and, depending on patient response, the maximum effect is reached after about 10 days from the start of r-hFSH administration.

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.

Clinical efficacy and safety in men

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

5.2 Pharmacokinetic properties

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% of the follitropin alfa dose is excreted in the urine.

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 SmPC.

In rabbits, the formulation reconstituted with 0.9% benzyl alcohol and 0.9% benzyl alcohol alone, both resulted in a slight haemorrhage and subacute inflammation after single subcutaneous injection or mild inflammatory and degenerative changes after single intramuscular injection respectively.

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
Phosphoric acid, concentrated (for pH adjustment)
Sodium hydroxide (for pH adjustment)

Solvent

Water for injections
Benzyl alcohol

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

The reconstituted solution is stable for 28 days at or below 25°C.

6.4 Special precautions for storage

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

After reconstitution, do not store above 25°C. Do not freeze. Store in the original container, 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 flip-off cap. The solvent for reconstitution is presented in 2 mL pre-filled syringes (Type I glass) with a rubber stopper. The administration syringes made of polypropylene with a stainless steel pre-fixed needle are also provided.

The medicinal product is supplied as a pack of 1 vial of powder with 1 pre-filled syringe of solvent for reconstitution and 15 disposable syringes for administration graduated in FSH units.

6.6 Special precautions for disposal and other handling

GONAL-f 1050 IU/1.75 mL powder must be reconstituted with the 2 mL solvent provided before use.

GONAL-f 1050 IU/1.75 mL powder must not be reconstituted with any other GONAL-f containers.

The solvent pre-filled syringe provided should be used for reconstitution only and then disposed of in accordance with local requirements. A set of administration syringes graduated in FSH units is supplied in the GONAL-f multidose box. Alternatively, a 1 mL syringe, graduated in mL, with

pre-fixed needle for subcutaneous administration could be used (see section “How to prepare and use the GONAL-f powder and solvent” in the package leaflet).

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.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/95/001/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 1995.

Date of latest renewal: 20 October 2010.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

GONAL-f 450 IU/0.75 mL powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each multidose vial contains 44 micrograms of follitropin alfa* (equivalent to 600 IU), in order to deliver 33 micrograms (equivalent to 450 IU) in 0.75 mL. Each mL of the reconstituted solution contains 600 IU.

* recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

Excipient with known effect: The reconstituted solution contains 9.45 mg benzyl alcohol per mL.

For the 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 to 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.
- GONAL-f in association with a luteinising hormone (LH) preparation is indicated for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men

- GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.

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.

Bioequivalence has been demonstrated between equivalent doses of the monodose presentation and the multidose presentation of GONAL-f.

The following table states the volume to be administered to deliver the prescribed dose:

Dose (IU)	Volume to be injected (mL)
75	0.13
150	0.25
225	0.38
300	0.50
375	0.63
450	0.75

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 to 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 estrogen 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 (r-hCG) or 5 000 IU, up to 10 000 IU hCG should be administered 24 to 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 to 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 estrogen 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 r-hCG or 5 000 IU up to 10 000 IU hCG is administered 24 to 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 to 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.

Women with severe LH and FSH deficiency

In LH and FSH deficient women, the objective of GONAL-f therapy in association with a luteinising hormone (LH) preparation is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). GONAL-f should be given as a course of daily injections simultaneously with lutropin alfa. If the patient is amenorrhoeic and has low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75 to 150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and estrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7- to 14-day intervals and preferably by 37.5 to 75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.

When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG should be administered 24 to 48 hours after the last GONAL-f and lutropin alfa injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Men with hypogonadotropic hypogonadism

GONAL-f should be given at a dose of 150 IU three times a week, concomitantly 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.

Special populations

Elderly

There is no relevant use of GONAL-f in the elderly population. Safety and efficacy 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 use. The injection should be given at the same time each day.

The first injection of GONAL-f should be performed under direct medical supervision. Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

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

Due to a local reactivity to benzyl alcohol, the same site of injection should not be used on consecutive days.

Individual reconstituted vials should be for single patient use only.

For instructions on reconstitution of the medicinal product see section 6.6 and the package leaflet.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- tumours of the hypothalamus or pituitary gland
- ovarian enlargement or ovarian cyst unrelated to polycystic ovarian disease and of unknown origin
- gynaecological haemorrhages of unknown origin
- ovarian, uterine or mammary carcinoma

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 care 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 estradiol levels, on a regular basis. There may be a degree of inter-patient 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

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 as 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- to 14-day intervals and preferably with 37.5 to 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, 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 estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

Adherence to recommended GONAL-f dose 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 estradiol 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 estradiol 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. 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 reaches its maximum at about seven to ten 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

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 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 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 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

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.

Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response.

Sodium content

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

Solvent containing benzyl alcohol

Following reconstitution with the solvent provided, this medicinal product contains 1.23 mg benzyl alcohol in each 75 IU dose, which is equivalent to 9.45 mg/mL. Benzyl alcohol may cause allergic reactions.

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.

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.

Breast-feeding

GONAL-f is not indicated during breast-feeding.

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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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) has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

Thromboembolism may occur very rarely (see section 4.4).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$), very rare ($< 1/10\,000$).

Treatment in women

Immune system disorders

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

Nervous system disorders

Very common: Headache

Vascular disorders

Very rare: Thromboembolism (both in association with and separate from OHSS)

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

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

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)

Treatment in men

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

Skin and subcutaneous tissue disorders

Common: Acne

Reproductive system and breast disorders

Common: Gynaecomastia, varicocele

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)

Investigations

Common: Weight gain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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 systems, gonadotropins, ATC code: G03GA05.

Mechanism of action

Follicle stimulating hormone (FSH) and luteinising hormone (LH) are secreted from the anterior pituitary gland in response to GnRH and play a complementary role in follicle development and ovulation. FSH stimulates the development of ovarian follicles, while LH action is involved in follicle development, steroidogenesis and maturation.

Pharmacodynamic effects

Inhibin and estradiol (E2) levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while E2 levels take more time, and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after 4 to 5 days of r-hFSH daily dosing, and, depending on patient response, the maximum effect is reached after about 10 days from the start of r-hFSH administration.

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.

Clinical efficacy and safety in men

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

5.2 Pharmacokinetic properties

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% of the follitropin alfa dose is excreted in the urine.

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 SmPC.

In rabbits, the formulation reconstituted with 0.9% benzyl alcohol and 0.9% benzyl alcohol alone, both resulted in a slight haemorrhage and subacute inflammation after single subcutaneous injection or mild inflammatory and degenerative changes after single intramuscular injection respectively.

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
Phosphoric acid, concentrated (for pH adjustment)
Sodium hydroxide (for pH adjustment)

Solvent

Water for injections
Benzyl alcohol

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

The reconstituted solution is stable for 28 days at or below 25°C.

6.4 Special precautions for storage

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

After reconstitution, do not store above 25°C. Do not freeze. Store in the original container, 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 flip-off cap. The solvent for reconstitution is presented in 1 mL pre-filled syringes (Type I glass) with a rubber stopper. The administration syringes made of polypropylene with a stainless steel pre-fixed needle are also provided.

The medicinal product is supplied as a pack of 1 vial of powder with 1 pre-filled syringe of solvent for reconstitution and 6 disposable syringes for administration graduated in FSH units.

6.6 Special precautions for disposal and other handling

GONAL-f 450 IU/0.75 mL powder must be reconstituted with the 1 mL solvent provided before use.

GONAL-f 450 IU/0.75 mL powder must not be reconstituted with any other GONAL-f containers.

The solvent pre-filled syringe provided should be used for reconstitution only and then disposed of in accordance with local requirements. A set of administration syringes graduated in FSH units is supplied in the GONAL-f multidose box. Alternatively, a 1 mL syringe, graduated in mL, with

pre-fixed needle for subcutaneous administration could be used (see section “How to prepare and use the GONAL-f powder and solvent” in the package leaflet).

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.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/95/001/031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 1995.

Date of latest renewal: 20 October 2010.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

GONAL-f 150 IU/0.24 mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled multidose pen contains 150 IU (equivalent to 11 micrograms) of follitropin alfa* in 0.24 mL solution.

* recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

Clear colourless solution.

The pH of the solution is 6.7 to 7.3.

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.
- GONAL-f in association with a luteinising hormone (LH) preparation is indicated for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men

- GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.

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.

Patients must be provided with the correct number of pens for their treatment course and educated to use the proper injection techniques.

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.

Bioequivalence has been demonstrated between equivalent doses of the monodose presentation and the multidose presentation of GONAL-f.

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 to 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 estrogen 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 (r-hCG) or 5 000 IU, up to 10 000 IU hCG should be administered 24 to 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 to 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 estrogen 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 r-hCG or 5 000 IU up to 10 000 IU hCG is administered 24 to 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 to 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.

Women with severe LH and FSH deficiency

In LH and FSH deficient women, the objective of GONAL-f therapy in association with a luteinising hormone (LH) preparation is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). GONAL-f should be given as a course of daily injections simultaneously with lutropin alfa. If the patient is amenorrhoeic and has low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75 to 150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and estrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7- to 14-day intervals and preferably by 37.5 to 75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.

When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG should be administered 24 to 48 hours after the last GONAL-f and lutropin alfa injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Men with hypogonadotropic hypogonadism

GONAL-f should be given at a dose of 150 IU three times a week, concomitantly 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.

Special populations

Elderly

There is no relevant use of GONAL-f in the elderly population. Safety and efficacy 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 use. The injection should be given at the same time each day.

The first injection of GONAL-f should be performed under direct medical supervision. Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

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.

For instructions on the administration with the pre-filled pen, see section 6.6 and the “Instructions for use”.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- tumours of the hypothalamus or pituitary gland
- ovarian enlargement or ovarian cyst unrelated to polycystic ovarian disease and of unknown origin
- gynaecological haemorrhages of unknown origin
- ovarian, uterine or mammary carcinoma

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 care 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 estradiol levels, on a regular basis. There may be a degree of inter-patient 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

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 as 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- to 14-day intervals and preferably with 37.5 to 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, 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 estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

Adherence to recommended GONAL-f dose 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 estradiol 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 estradiol level $> 5\,500\text{ pg/mL}$ or $> 20\,200\text{ pmol/L}$ 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. 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 reaches its maximum at about seven to ten 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

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 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 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 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

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.

Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response.

Sodium content

GONAL-f contains less than 1 mmol sodium (23 mg) per dose, i.e. it is 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.

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.

Breast-feeding

GONAL-f is not indicated during breast-feeding.

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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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) has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

Thromboembolism may occur very rarely (see section 4.4).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$), very rare ($< 1/10\,000$).

Treatment in women

Immune system disorders

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

Nervous system disorders

Very common: Headache

Vascular disorders

Very rare: Thromboembolism (both in association with and separate from OHSS)

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

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

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)

Treatment in men

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

Skin and subcutaneous tissue disorders

Common: Acne

Reproductive system and breast disorders

Common: Gynaecomastia, varicocele

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)

Investigations

Common: Weight gain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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 systems, gonadotropins, ATC code: G03GA05.

Mechanism of action

Follicle stimulating hormone (FSH) and luteinising hormone (LH) are secreted from the anterior pituitary gland in response to GnRH and play a complementary role in follicle development and ovulation. FSH stimulates the development of ovarian follicles, while LH action is involved in follicle development, steroidogenesis and maturation.

Pharmacodynamic effects

Inhibin and estradiol (E2) levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while E2 levels take more time, and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after 4 to 5 days of r-hFSH daily dosing, and, depending on patient response, the maximum effect is reached after about 10 days from the start of r-hFSH administration.

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.

Clinical efficacy and safety in men

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

5.2 Pharmacokinetic properties

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% of the follitropin alfa dose is excreted in the urine.

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 SmPC.

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

Poloxamer 188
Sucrose
Methionine
Sodium dihydrogen phosphate monohydrate
Disodium phosphate dihydrate
m-Cresol
Phosphoric acid, concentrated (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Once opened, the medicinal product should be stored between 2°C and 25°C for a maximum of 28 days. The patient should write on the GONAL-f pre-filled pen the day of the first use.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.

Before opening and within its shelf life, the medicinal product may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months. The product must be discarded if it has not been used within these 3 months.

Keep the cap on the pen, in order to protect from light.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

0.24 mL of solution for injection in 3 mL cartridge (Type I glass), with a plunger stopper (halobutyl rubber) and an aluminium crimp cap with a black rubber inlay.

Pack of one pre-filled pen and 4 needles to be used with the pen for administration.

6.6 Special precautions for disposal and other handling

See the "Instructions for use".

Prior to subcutaneous administration and if the pre-filled pen is kept refrigerated, the pre-filled pen should be allowed to sit at room temperature for at least 30 minutes before injecting to allow the medicinal product to reach room temperature. The pen must not be warmed by using a microwave or other heating element.

The solution should not be administered if it contains particles or is not clear.

Any unused solution must be discarded not later than 28 days after first opening.

GONAL-f 150 IU/0.24 mL solution for injection in pre-filled pen is not designed to allow the cartridge to be removed.

Discard used needles immediately after injection.

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

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/95/001/036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 1995.

Date of latest renewal: 20 October 2010.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

GONAL-f 300 IU/0.48 mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled multidose pen contains 300 IU (equivalent to 22 micrograms) of follitropin alfa* in 0.48 mL solution.

* recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

Clear colourless solution.

The pH of the solution is 6.7 to 7.3.

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.
- GONAL-f in association with a luteinising hormone (LH) preparation is indicated for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men

- GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.

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.

Patients must be provided with the correct number of pens for their treatment course and educated to use the proper injection techniques.

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.

Bioequivalence has been demonstrated between equivalent doses of the monodose presentation and the multidose presentation of GONAL-f.

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 to 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 estrogen 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 (r-hCG) or 5 000 IU, up to 10 000 IU hCG should be administered 24 to 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 to 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 estrogen 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 r-hCG or 5 000 IU up to 10 000 IU hCG is administered 24 to 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 to 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.

Women with severe LH and FSH deficiency

In LH and FSH deficient women, the objective of GONAL-f therapy in association with a luteinising hormone (LH) preparation is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). GONAL-f should be given as a course of daily injections simultaneously with lutropin alfa. If the patient is amenorrhoeic and has low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75 to 150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and estrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7- to 14-day intervals and preferably by 37.5 to 75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.

When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG should be administered 24 to 48 hours after the last GONAL-f and lutropin alfa injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Men with hypogonadotropic hypogonadism

GONAL-f should be given at a dose of 150 IU three times a week, concomitantly 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.

Special populations

Elderly

There is no relevant use of GONAL-f in the elderly population. Safety and efficacy 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 use. The injection should be given at the same time each day.

The first injection of GONAL-f should be performed under direct medical supervision. Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

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.

For instructions on the administration with the pre-filled pen, see section 6.6 and the “Instructions for use”.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- tumours of the hypothalamus or pituitary gland
- ovarian enlargement or ovarian cyst unrelated to polycystic ovarian disease and of unknown origin
- gynaecological haemorrhages of unknown origin
- ovarian, uterine or mammary carcinoma

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 care 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 estradiol levels, on a regular basis. There may be a degree of inter-patient 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

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 as 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- to 14-day intervals and preferably with 37.5 to 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, 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 estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

Adherence to recommended GONAL-f dose 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 estradiol 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 estradiol level $> 5\,500\text{ pg/mL}$ or $> 20\,200\text{ pmol/L}$ 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. 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 reaches its maximum at about seven to ten 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

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 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 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 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

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.

Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response.

Sodium content

GONAL-f contains less than 1 mmol sodium (23 mg) per dose, i.e. it is 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.

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.

Breast-feeding

GONAL-f is not indicated during breast-feeding.

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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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) has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

Thromboembolism may occur very rarely (see section 4.4).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$), very rare ($< 1/10\,000$).

Treatment in women

Immune system disorders

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

Nervous system disorders

Very common: Headache

Vascular disorders

Very rare: Thromboembolism (both in association with and separate from OHSS)

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

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

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)

Treatment in men

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

Skin and subcutaneous tissue disorders

Common: Acne

Reproductive system and breast disorders

Common: Gynaecomastia, varicocele

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)

Investigations

Common: Weight gain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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 systems, gonadotropins, ATC code: G03GA05.

Mechanism of action

Follicle stimulating hormone (FSH) and luteinising hormone (LH) are secreted from the anterior pituitary gland in response to GnRH and play a complementary role in follicle development and ovulation. FSH stimulates the development of ovarian follicles, while LH action is involved in follicle development, steroidogenesis and maturation.

Pharmacodynamic effects

Inhibin and estradiol (E2) levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while E2 levels take more time, and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after 4 to 5 days of r-hFSH daily dosing, and, depending on patient response, the maximum effect is reached after about 10 days from the start of r-hFSH administration.

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.

Clinical efficacy and safety in men

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

5.2 Pharmacokinetic properties

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% of the follitropin alfa dose is excreted in the urine.

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 SmPC.

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

Poloxamer 188
Sucrose
Methionine
Sodium dihydrogen phosphate monohydrate
Disodium phosphate dihydrate
m-Cresol
Phosphoric acid, concentrated (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Once opened, the medicinal product should be stored between 2°C and 25°C for a maximum of 28 days. The patient should write on the GONAL-f pre-filled pen the day of the first use.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.

Before opening and within its shelf life, the medicinal product may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months. The product must be discarded if it has not been used within these 3 months.

Keep the cap on the pen, in order to protect from light.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

0.48 mL of solution for injection in 3 mL cartridge (Type I glass), with a plunger stopper (halobutyl rubber) and an aluminium crimp cap with a black rubber inlay.

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

6.6 Special precautions for disposal and other handling

See the "Instructions for use".

Prior to subcutaneous administration and if the pre-filled pen is kept refrigerated, the pre-filled pen should be allowed to sit at room temperature for at least 30 minutes before injecting to allow the medicinal product to reach room temperature. The pen must not be warmed by using a microwave or other heating element.

The solution should not be administered if it contains particles or is not clear.

Any unused solution must be discarded not later than 28 days after first opening.

GONAL-f 300 IU/0.48 mL solution for injection in pre-filled pen is not designed to allow the cartridge to be removed.

Discard used needles immediately after injection.

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

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/95/001/033

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 1995.

Date of latest renewal: 20 October 2010.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

GONAL-f 450 IU/0.72 mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled multidose pen contains 450 IU (equivalent to 33 micrograms) of follitropin alfa* in 0.72 mL solution.

* recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

Clear colourless solution.

The pH of the solution is 6.7 to 7.3.

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.
- GONAL-f in association with a luteinising hormone (LH) preparation is indicated for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men

- GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.

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.

Patients must be provided with the correct number of pens for their treatment course and educated to use the proper injection techniques.

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.

Bioequivalence has been demonstrated between equivalent doses of the monodose presentation and the multidose presentation of GONAL-f.

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 to 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 estrogen 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 (r-hCG) or 5 000 IU, up to 10 000 IU hCG should be administered 24 to 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 to 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 estrogen 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 r-hCG or 5 000 IU up to 10 000 IU hCG is administered 24 to 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 to 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.

Women with severe LH and FSH deficiency

In LH and FSH deficient women, the objective of GONAL-f therapy in association with a luteinising hormone (LH) preparation is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). GONAL-f should be given as a course of daily injections simultaneously with lutropin alfa. If the patient is amenorrhoeic and has low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75 to 150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and estrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7- to 14-day intervals and preferably by 37.5 to 75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.

When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG should be administered 24 to 48 hours after the last GONAL-f and lutropin alfa injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Men with hypogonadotropic hypogonadism

GONAL-f should be given at a dose of 150 IU three times a week, concomitantly 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.

Special populations

Elderly

There is no relevant use of GONAL-f in the elderly population. Safety and efficacy 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 use. The injection should be given at the same time each day.

The first injection of GONAL-f should be performed under direct medical supervision. Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

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.

For instructions on the administration with the pre-filled pen, see section 6.6 and the “Instructions for use”.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- tumours of the hypothalamus or pituitary gland
- ovarian enlargement or ovarian cyst unrelated to polycystic ovarian disease and of unknown origin
- gynaecological haemorrhages of unknown origin
- ovarian, uterine or mammary carcinoma

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 care 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 estradiol levels, on a regular basis. There may be a degree of inter-patient 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

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 as 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- to 14-day intervals and preferably with 37.5 to 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, 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 estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

Adherence to recommended GONAL-f dose 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 estradiol 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 estradiol 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. 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 reaches its maximum at about seven to ten 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

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 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 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 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

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.

Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response.

Sodium content

GONAL-f contains less than 1 mmol sodium (23 mg) per dose, i.e. it is 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.

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.

Breast-feeding

GONAL-f is not indicated during breast-feeding.

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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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) has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

Thromboembolism may occur very rarely (see section 4.4).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$), very rare ($< 1/10\,000$).

Treatment in women

Immune system disorders

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

Nervous system disorders

Very common: Headache

Vascular disorders

Very rare: Thromboembolism (both in association with and separate from OHSS)

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

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

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)

Treatment in men

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

Skin and subcutaneous tissue disorders

Common: Acne

Reproductive system and breast disorders

Common: Gynaecomastia, varicocele

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)

Investigations

Common: Weight gain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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 systems, gonadotropins, ATC code: G03GA05.

Mechanism of action

Follicle stimulating hormone (FSH) and luteinising hormone (LH) are secreted from the anterior pituitary gland in response to GnRH and play a complementary role in follicle development and ovulation. FSH stimulates the development of ovarian follicles, while LH action is involved in follicle development, steroidogenesis and maturation.

Pharmacodynamic effects

Inhibin and estradiol (E2) levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while E2 levels take more time, and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after 4 to 5 days of r-hFSH daily dosing, and, depending on patient response, the maximum effect is reached after about 10 days from the start of r-hFSH administration.

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.

Clinical efficacy and safety in men

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

5.2 Pharmacokinetic properties

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% of the follitropin alfa dose is excreted in the urine.

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 SmPC.

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

Poloxamer 188
Sucrose
Methionine
Sodium dihydrogen phosphate monohydrate
Disodium phosphate dihydrate
m-Cresol
Phosphoric acid, concentrated (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Once opened, the medicinal product should be stored between 2°C and 25°C for a maximum of 28 days. The patient should write on the GONAL-f pre-filled pen the day of the first use.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.

Before opening and within its shelf life, the medicinal product may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months. The product must be discarded if it has not been used within these 3 months.

Keep the cap on the pen, in order to protect from light.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

0.72 mL of solution for injection in 3 mL cartridge (Type I glass), with a plunger stopper (halobutyl rubber) and an aluminium crimp cap with a black rubber inlay.

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

6.6 Special precautions for disposal and other handling

See the "Instructions for use".

Prior to subcutaneous administration and if the pre-filled pen is kept refrigerated, the pre-filled pen should be allowed to sit at room temperature for at least 30 minutes before injecting to allow the medicinal product to reach room temperature. The pen must not be warmed by using a microwave or other heating element.

The solution should not be administered if it contains particles or is not clear.

Any unused solution must be discarded not later than 28 days after first opening.

GONAL-f 450 IU/0.72 mL solution for injection in pre-filled pen is not designed to allow the cartridge to be removed.

Discard used needles immediately after injection.

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

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/95/001/034

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 1995.

Date of latest renewal: 20 October 2010.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

GONAL-f 900 IU/1.44 mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled multidose pen contains 900 IU (equivalent to 66 micrograms) of follitropin alfa* in 1.44 mL solution.

* recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

Clear colourless solution.

The pH of the solution is 6.7 to 7.3.

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.
- GONAL-f in association with a luteinising hormone (LH) preparation is indicated for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men

- GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.

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.

Patients must be provided with the correct number of pens for their treatment course and educated to use the proper injection techniques.

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.

Bioequivalence has been demonstrated between equivalent doses of the monodose presentation and the multidose presentation of GONAL-f.

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 to 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 estrogen 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 (r-hCG) or 5 000 IU, up to 10 000 IU hCG should be administered 24 to 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 to 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 estrogen 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 r-hCG or 5 000 IU up to 10 000 IU hCG is administered 24 to 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 to 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.

Women with severe LH and FSH deficiency

In LH and FSH deficient women, the objective of GONAL-f therapy in association with a luteinising hormone (LH) preparation is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). GONAL-f should be given as a course of daily injections simultaneously with lutropin alfa. If the patient is amenorrhoeic and has low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75 to 150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and estrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7- to 14-day intervals and preferably by 37.5 to 75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.

When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG should be administered 24 to 48 hours after the last GONAL-f and lutropin alfa injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Men with hypogonadotropic hypogonadism

GONAL-f should be given at a dose of 150 IU three times a week, concomitantly 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.

Special populations

Elderly

There is no relevant use of GONAL-f in the elderly population. Safety and efficacy 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 use. The injection should be given at the same time each day.

The first injection of GONAL-f should be performed under direct medical supervision. Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

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.

For instructions on the administration with the pre-filled pen, see section 6.6 and the “Instructions for use”.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- tumours of the hypothalamus or pituitary gland
- ovarian enlargement or ovarian cyst unrelated to polycystic ovarian disease and of unknown origin
- gynaecological haemorrhages of unknown origin
- ovarian, uterine or mammary carcinoma

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 care 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 estradiol levels, on a regular basis. There may be a degree of inter-patient 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

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 as 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- to 14-day intervals and preferably with 37.5 to 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, 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 estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

Adherence to recommended GONAL-f dose 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 estradiol 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 estradiol level $> 5\,500\text{ pg/mL}$ or $> 20\,200\text{ pmol/L}$ 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. 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 reaches its maximum at about seven to ten 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

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 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 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 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

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.

Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response.

Sodium content

GONAL-f contains less than 1 mmol sodium (23 mg) per dose, i.e. it is 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.

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.

Breast-feeding

GONAL-f is not indicated during breast-feeding.

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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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) has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

Thromboembolism may occur very rarely (see section 4.4).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$), very rare ($< 1/10\,000$).

Treatment in women

Immune system disorders

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

Nervous system disorders

Very common: Headache

Vascular disorders

Very rare: Thromboembolism (both in association with and separate from OHSS)

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

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

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)

Treatment in men

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

Skin and subcutaneous tissue disorders

Common: Acne

Reproductive system and breast disorders

Common: Gynaecomastia, varicocele

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)

Investigations

Common: Weight gain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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 systems, gonadotropins, ATC code: G03GA05.

Mechanism of action

Follicle stimulating hormone (FSH) and luteinising hormone (LH) are secreted from the anterior pituitary gland in response to GnRH and play a complementary role in follicle development and ovulation. FSH stimulates the development of ovarian follicles, while LH action is involved in follicle development, steroidogenesis and maturation.

Pharmacodynamic effects

Inhibin and estradiol (E2) levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while E2 levels take more time, and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after 4 to 5 days of r-hFSH daily dosing, and, depending on patient response, the maximum effect is reached after about 10 days from the start of r-hFSH administration.

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.

Clinical efficacy and safety in men

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

5.2 Pharmacokinetic properties

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% of the follitropin alfa dose is excreted in the urine.

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 SmPC.

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

Poloxamer 188
Sucrose
Methionine
Sodium dihydrogen phosphate monohydrate
Disodium phosphate dihydrate
m-Cresol
Phosphoric acid, concentrated (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Once opened, the medicinal product should be stored between 2°C and 25°C for a maximum of 28 days. The patient should write on the GONAL-f pre-filled pen the day of the first use.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.

Before opening and within its shelf life, the medicinal product may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months. The product must be discarded if it has not been used within these 3 months.

Keep the cap on the pen, in order to protect from light.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

1.44 mL of solution for injection in 3 mL cartridge (Type I glass), with a plunger stopper (halobutyl rubber) and an aluminium crimp cap with a black rubber inlay.

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

6.6 Special precautions for disposal and other handling

See the "Instructions for use".

Prior to subcutaneous administration and if the pre-filled pen is kept refrigerated, the pre-filled pen should be allowed to sit at room temperature for at least 30 minutes before injecting to allow the medicinal product to reach room temperature. The pen must not be warmed by using a microwave or other heating element.

The solution should not be administered if it contains particles or is not clear.

Any unused solution must be discarded not later than 28 days after first opening.

GONAL-f 900 IU/1.44 mL solution for injection in pre-filled pen is not designed to allow the cartridge to be removed.

Discard used needles immediately after injection.

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

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/95/001/035

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 1995.

Date of latest renewal: 20 October 2010.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE
AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Merck Serono S.A.
Succursale d'Aubonne
Zone Industrielle de l'Ouriettaz
1170 Aubonne
Switzerland

or

Merck S.L.
C/ Batanes 1
28760 Tres Cantos (Madrid)
Spain

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**GONAL-f 75 IU, BOX OF 1, 5, 10 VIALS AND 1, 5, 10 PRE-FILLED SYRINGES****1. NAME OF THE MEDICINAL PRODUCT**

GONAL-f 75 IU powder and solvent for solution for injection
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 5.5 micrograms follitropin alfa equivalent to 75 IU. Each mL of the reconstituted solution contains 75 IU.

3. LIST OF EXCIPIENTS

Excipients: sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, methionine, polysorbate 20, concentrated phosphoric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).
Solvent for solution for injection: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection.
1 pre-filled syringe of 1 mL solvent.

5 vials of powder for solution for injection.
5 pre-filled syringes of 1 mL solvent.

10 vials of powder for solution for injection.
10 pre-filled syringes of 1 mL solvent.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/95/001/025 1 vial of powder for solution for injection
1 pre-filled syringe of solvent

EU/1/95/001/026 5 vials of powder for solution for injection
5 pre-filled syringes of solvent

EU/1/95/001/027 10 vials of powder for solution for injection
10 pre-filled syringes of solvent

13. BATCH NUMBER

Batch
Solvent Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

gonal-f 75 iu

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**GONAL-F 75 IU, VIAL LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

GONAL-f 75 IU powder for solution for injection
follitropin alfa
S.C.

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

75 UI

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS GONAL-f 75 IU, SOLVENT PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Solvent for powder for solution for injection for GONAL-f
water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

1 mL/pre-filled syringe

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**GONAL-f 1050 IU/1.75 mL, BOX OF 1 VIAL AND 1 PRE-FILLED SYRINGE****1. NAME OF THE MEDICINAL PRODUCT**

GONAL-f 1050 IU/1.75 mL powder and solvent for solution for injection
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each multidose vial contains 87 micrograms follitropin alfa equivalent to 1 200 IU. Each mL of the reconstituted solution contains 600 IU.

3. LIST OF EXCIPIENTS

Excipients: sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, concentrated phosphoric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).
Solvent for solution for injection: water for injections, benzyl alcohol 0.9%.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection.
1 pre-filled syringe of 2 mL solvent.
15 disposable syringes for administration graduated in FSH units.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For multiple injections only.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The solvent pre-filled syringe provided should be used for reconstitution only.
The reconstituted vial should be for single patient use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

After reconstitution, do not store above 25°C. Do not freeze. Store in the original container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution after 28 days.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/95/001/021 1 vial of powder for solution for injection
 1 pre-filled syringe of solvent
 15 disposable syringes

13. BATCH NUMBER

Batch
Solvent Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

gonal-f 1050 iu

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**GONAL-f 1050 IU/1.75 mL, VIAL LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

GONAL-f 1050 IU/1.75 mL powder for solution for injection
follitropin alfa
S.C.

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP

4. DATE OF RECONSTITUTION

Date:

5. BATCH NUMBER

Batch

6. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1200 IU/vial

7. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**GONAL-f 1050 IU/1.75 mL, SOLVENT PRE-FILLED SYRINGE LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Solvent for use with GONAL-f 1050 IU/1.75 mL
water for injections, benzyl alcohol 0.9%

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mL/pre-filled syringe

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**GONAL-f 450 IU/0.75 mL, BOX OF 1 VIAL AND 1 PRE-FILLED SYRINGE****1. NAME OF THE MEDICINAL PRODUCT**

GONAL-f 450 IU/0.75 mL powder and solvent for solution for injection
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each multidose vial contains 44 micrograms follitropin alfa equivalent to 600 IU. Each mL of the reconstituted solution contains 600 IU.

3. LIST OF EXCIPIENTS

Excipients: sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, concentrated phosphoric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).
Solvent for solution for injection: water for injections, benzyl alcohol 0.9%.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection.
1 pre-filled syringe of 1 mL solvent.
6 disposable syringes for administration graduated in FSH units.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For multiple injections only.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The solvent pre-filled syringe provided should be used for reconstitution only.
The reconstituted vial should be for single patient use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

After reconstitution, do not store above 25°C. Do not freeze. Store in the original container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution after 28 days.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/95/001/031 1 vial of powder for solution for injection
 1 pre-filled syringe of solvent
 6 disposable syringes

13. BATCH NUMBER

Batch
Solvent Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

gonal-f 450 iu

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**GONAL-f 450 IU/0.75 ML, VIAL LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

GONAL-f 450 IU/0.75 mL powder for solution for injection
follitropin alfa
S.C.

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP

4. DATE OF RECONSTITUTION

Date:

5. BATCH NUMBER

Batch

6. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

600 IU/vial

7. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS GONAL-f 450 IU/0.75 mL, SOLVENT PRE-FILLED SYRINGE LABEL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Solvent for use with GONAL-f 450 IU/0.75 mL
water for injections, benzyl alcohol 0.9%

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

1 mL/pre-filled syringe

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**GONAL-f 150 IU/0.24 ML PEN, BOX OF 1 PRE-FILLED PEN****1. NAME OF THE MEDICINAL PRODUCT**

GONAL-f 150 IU/0.24 mL solution for injection in pre-filled pen
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled multidose pen contains 150 IU (equivalent to 11 micrograms) of follitropin alfa in 0.24 mL.

3. LIST OF EXCIPIENTS

Excipients: Poloxamer 188, sucrose, methionine, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, m-cresol, concentrated phosphoric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen.
1 multidose pre-filled pen
4 injection needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the cap on the pen, in order to protect from light.

Before opening and within its shelf-life, the medicine may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months and must be discarded afterwards.

Once opened, the medicine should be stored between 2°C and 25°C for a maximum of 28 days.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/95/001/036 solution for injection in pre-filled pen
4 needles

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

gonal-f 150 iu/0.24 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

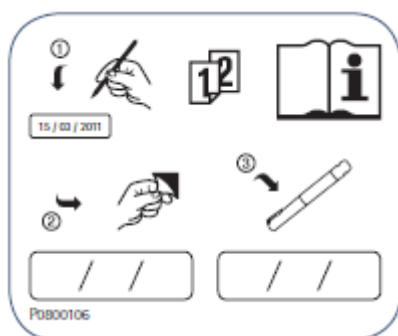
18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
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PARTICULARS TO APPEAR ON THE PEN

GONAL-f 150 IU/0.24 ML PEN, STICKER

A sticker will be added to allow the patient to write the day of first use.



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**GONAL-f 150 IU/0.24 ML PEN, PEN LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

GONAL-f 150 IU/0.24 mL solution for injection in pre-filled pen
follitropin alfa
Subcutaneous use

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP
Shelf-life after first use: 28 days

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 IU/0.24 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**GONAL-f 300 IU/0.48 ML PEN, BOX OF 1 PRE-FILLED PEN****1. NAME OF THE MEDICINAL PRODUCT**

GONAL-f 300 IU/0.48 mL solution for injection in pre-filled pen
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled multidose pen contains 300 IU (equivalent to 22 micrograms) of follitropin alfa in 0.48 mL.

3. LIST OF EXCIPIENTS

Excipients: Poloxamer 188, sucrose, methionine, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, m-cresol, concentrated phosphoric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen.
1 multidose pre-filled pen
8 injection needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the cap on the pen, in order to protect from light.

Before opening and within its shelf-life, the medicine may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months and must be discarded afterwards.

Once opened, the medicine should be stored between 2°C and 25°C for a maximum of 28 days.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/95/001/033 solution for injection in pre-filled pen
8 needles

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

gonal-f 300 iu/0.48 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

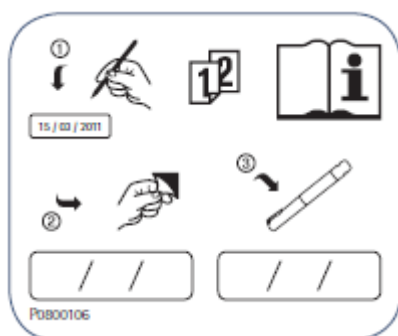
18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
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PARTICULARS TO APPEAR ON THE PEN

GONAL-f 300 IU/0.48 ML PEN, STICKER

A sticker will be added to allow the patient to write the day of first use.



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**GONAL-f 300 IU/0.48 ML PEN, PEN LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

GONAL-f 300 IU/0.48 mL solution for injection in pre-filled pen
follitropin alfa
Subcutaneous use

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP
Shelf-life after first use: 28 days

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 IU/0.48 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**GONAL-f 450 IU/0.72 ML, BOX OF 1 PRE-FILLED PEN****1. NAME OF THE MEDICINAL PRODUCT**

GONAL-f 450 IU/0.72 mL solution for injection in pre-filled pen
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled multidose pen contains 450 IU (equivalent to 33 micrograms) of follitropin alfa in 0.72 mL.

3. LIST OF EXCIPIENTS

Excipients: Poloxamer 188, sucrose, methionine, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, m-cresol, concentrated phosphoric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen.
1 multidose pre-filled pen
12 injection needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the cap on the pen, in order to protect from light.

Before opening and within its shelf-life, the medicine may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months and must be discarded afterwards.

Once opened, the medicine should be stored between 2°C and 25°C for a maximum of 28 days.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/95/001/034 solution for injection in pre-filled pen
12 needles

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

gonal-f 450 iu/0.72 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

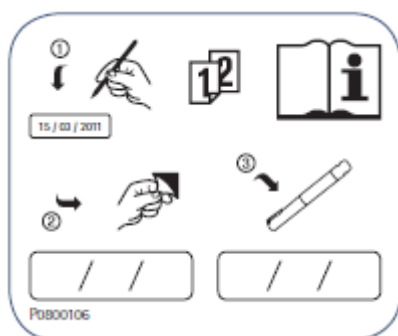
18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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PARTICULARS TO APPEAR ON THE PEN

GONAL-f 450 IU/0.72 ML PEN, STICKER

A sticker will be added to allow the patient to write the day of first use.



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**GONAL-f 450 IU/0.72 ML PEN, PEN LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

GONAL-f 450 IU/0.72 mL solution for injection in pre-filled pen
follitropin alfa
Subcutaneous use

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP
Shelf-life after first use: 28 days

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

450 IU/0.72 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**GONAL-f 900 IU/1.44 ML PEN, BOX OF 1 PRE-FILLED PEN****1. NAME OF THE MEDICINAL PRODUCT**

GONAL-f 900 IU/1.44 mL solution for injection in pre-filled pen
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled multidose pen contains 900 IU (equivalent to 66 micrograms) of follitropin alfa in 1.44 mL.

3. LIST OF EXCIPIENTS

Excipients: Poloxamer 188, sucrose, methionine, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, m-cresol, concentrated phosphoric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen.
1 multidose pre-filled pen
20 injection needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the cap on the pen, in order to protect from light.

Before opening and within its shelf-life, the medicine may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months and must be discarded afterwards.

Once opened, the medicine should be stored between 2°C and 25°C for a maximum of 28 days.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/95/001/035 solution for injection in pre-filled pen
20 needles

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

gonal-f 900 iu/1.44 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

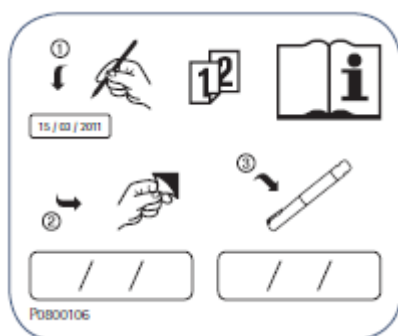
18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
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PARTICULARS TO APPEAR ON THE PEN

GONAL-f 900 IU/1.44 ML PEN, STICKER

A sticker will be added to allow the patient to write the day of first use.



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**GONAL-f 900 IU/1.44 ML PEN, PEN LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

GONAL-f 900 IU/1.44 mL solution for injection in pre-filled pen
follitropin alfa
Subcutaneous use

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP
Shelf-life after first use: 28 days

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

900 IU/1.44 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

GONAL-f 75 IU powder and solvent for solution for injection follitropin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What GONAL-f is and what it is used for
2. What you need to know before you use GONAL-f
3. How to use GONAL-f
4. Possible side effects
5. How to store GONAL-f
6. Contents of the pack and other information
How to prepare and use the GONAL-f powder and solvent

1. What GONAL-f is and what it is used for

What GONAL-f is

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.

What GONAL-f is used for

In adult women, GONAL-f is used:

- to help release an egg from the ovary (ovulation) in women that cannot ovulate and that did not respond to treatment with a medicine called “clomiphene citrate”.
- together with another medicine called “lutropin alfa” (“luteinising hormone” or LH) to help release egg from the ovary (ovulation) in women whose body is producing very little gonadotropins (FSH and LH).
- to help develop several follicles (each containing an egg) in women undergoing assisted reproductive technology procedures (procedures that may help you to become pregnant) such as “*in vitro* fertilisation”, “gamete intra-fallopian transfer” or “zygote intra-fallopian transfer”.

In adult men, GONAL-f is used:

- together with another medicine called “human chorionic gonadotropin” (hCG) to help produce sperm in men that are infertile due to a low level of certain hormones.

2. What you need to know before you use GONAL-f

You and your partner’s fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility disorders.

Do not use GONAL-f

- if you are allergic to follicle stimulating hormone or any of the other ingredients of this medicine listed in section 6.
- if you have a tumour in your hypothalamus or pituitary gland (both are parts of the brain).
- if you are **a woman**:
 - with large ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
 - with unexplained vaginal bleeding.
 - with cancer in your ovaries, womb or breasts.
 - with a condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), or malformed reproductive organs.
- if you are **a man**:
 - with damaged testicles that cannot be healed.

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Gonal-f.

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).

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.

Ovarian hyper-stimulation syndrome (OHSS)

If you are a woman, this medicine increases your risk of developing OHSS. This is when your follicles develop too much and become large cysts. If you get lower abdominal pain, gain any weight rapidly, feel sick or are vomiting or if you have difficulty in breathing, talk to your doctor straight away who might ask you to stop using this medicine (see section 4).

In case you are not ovulating, and if the recommended dose and schedule of administration are adhered to, the occurrence of OHSS is less likely. GONAL-f treatment seldom causes severe OHSS unless the medicine that is used for final follicular maturation (containing human chorionic gonadotropin, 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.

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. When undergoing assisted reproductive technology, the risk of having a multiple pregnancy is related to your age, the quality and the number of fertilised eggs or embryos placed inside you.

Miscarriage

When undergoing assisted reproductive technology or stimulation of your ovaries to produce eggs, you are more likely to have a miscarriage than the average woman.

Blood clotting problems (thromboembolic events)

If you had in the past or recently blood clots in the leg or in the lung, or a heart attack or stroke, or if those happened in your family, then you might have a higher risk that these problems occur or become worse with GONAL-f treatment.

Men with too much FSH in their blood

If you are a man, having too much FSH in your blood can be a sign of damaged testicles. GONAL-f usually does not work if you have this problem.

If your doctor decides to try GONAL-f treatment, to monitor the treatment, they may ask you to provide semen for analysis 4 to 6 months after starting treatment.

Children and adolescents

GONAL-f is not for use in children and adolescents below 18 years old.

Other medicines and GONAL-f

Tell your doctor if you are taking, have recently taken or might take any other medicines.

- If you use GONAL-f with other medicines which help ovulation (such as hCG or clomiphene citrate), this may increase the response of your follicles.
- If you use GONAL-f at the same time as a “gonadotropin-releasing hormone” (GnRH) agonist or antagonist (these medicines reduce your sex hormone levels and stop you ovulating) you may need a higher dose of GONAL-f to produce follicles.

Pregnancy and breast-feeding

Do not use GONAL-f if you are pregnant or breast-feeding.

Driving and using machines

It is not expected that this medicine will affect your ability to drive and use machines.

GONAL-f contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially “sodium-free”.

3. How to use GONAL-f

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Using this medicine

- GONAL-f is intended to be given by injection just under the skin (subcutaneously).
- 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.
- If you administer GONAL-f to yourself, please carefully read and follow the instructions at the end of this leaflet called “How to prepare and use the GONAL-f powder and solution”.

How much to use

Your doctor will decide how much medicine you will take and how often. The doses described below are stated in International Units (IU).

Women

If you are not ovulating and have irregular or no periods.

- GONAL-f is usually given every day.
- If you have irregular periods, start using GONAL-f within the first 7 days of your menstrual cycle. If you do not have periods you can start using the medicine on any convenient day.
- The usual starting dose of GONAL-f is 75 to 150 IU each day.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- The maximum daily dose of GONAL-f is usually not higher than 225 IU.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last GONAL-f injection. The best time to have sex is on the day of the hCG injection and the day after.

If your doctor cannot see a desired response after 4 weeks, that treatment cycle with GONAL-f should be stopped. For the following treatment cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you have been diagnosed with very low levels of FSH and LH hormones

- The usual starting dose of GONAL-f is 75 to 150 IU together with 75 IU of lutropin alfa.
- You will use these two medicines each day for up to five weeks.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last injections of GONAL-f and lutropin alfa. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on your doctor’s judgment.

If your doctor cannot see a response after 5 weeks, that treatment cycle with GONAL-f should be stopped. For the following cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment with GONAL-f will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you need to develop several eggs for collection prior to any assisted reproductive technology

- The usual starting dose of GONAL-f is 150 to 225 IU each day, from day 2 or 3 of your treatment cycle.
- GONAL-f dose may be increased, depending on your response. The maximum daily dose is 450 IU.
- Treatment is continued until your eggs have developed to a desired point. This usually takes about 10 days but can take any time between 5 and 20 days. Your doctor will use blood tests and/or an ultrasound machine to check when this is.
- When your eggs are ready, you will be given a single injection of 250 micrograms “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special recombinant DNA technique), or 5 000 IU to 10 000 IU of hCG, 24 to 48 hours after the last GONAL-f injection. This gets your eggs ready for collection.

In other cases, your doctor may first stop you from ovulating by using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Then GONAL-f is started approximately two weeks after start of agonist treatment. The GONAL-f and GnRH agonist are then both given until your follicles develop as desired. For example, after two weeks of GnRH agonist treatment, 150 to 225 IU GONAL-f is administered for 7 days. The dose is then adjusted according to your ovarian response.

Men

- The usual dose of GONAL-f is 150 IU together with hCG.
- You will use these two medicines three times a week for at least 4 months.
- If you have not responded to treatment after 4 months, your doctor may suggest that you continue using these two medicines for at least 18 months.

If you use more GONAL-f than you should

The effects of taking too much GONAL-f are unknown. Nevertheless, one could expect ovarian hyper-stimulation syndrome (OHSS) to occur, which is described in section 4. However, the OHSS will only occur if hCG is also administered (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”).

If you forget to use GONAL-f

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.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects in women

- Lower abdominal pain together with nausea or vomiting may be the symptoms of ovarian hyper-stimulation syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed (see also in section 2. under “Ovarian hyper-stimulation syndrome (OHSS)”). This side effect is common (may affect up to 1 in 10 people).
- 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 side effect is uncommon (may affect up to 1 in 100 people).

- Complications of OHSS such as twisting of ovaries or blood clotting may occur rarely (may affect up to 1 in 1 000 people).
- Serious blood clotting complications (thromboembolic events) sometimes independent of OHSS may be found very rarely (may affect up to 1 in 10 000 people). This could cause chest pain, breathlessness, stroke or heart attack (see also in section 2. under “Blood clotting problems”).

Serious side effects in men and women

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing can sometimes be serious. This side effect is very rare (may affect up to 1 in 10 000 people).

If you notice any of the above-listed side effects, you should immediately contact your doctor who might ask you to stop using GONAL-f.

Other side effects in women

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

- Abdominal pain
- Feeling sick, vomiting, diarrhoea, abdominal cramps and bloating

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Other side effects in men

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

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

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty in breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GONAL-f

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial after EXP. The expiry date refers to the last day of that month.

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.

The medicine must be administered immediately after preparation.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

GONAL-f should not be administered as a mixture with other medicines in the same injection, except for lutropin alfa. Studies have shown that these two medicines can be mixed and injected together, without either product being adversely affected.

6. Contents of the pack and other information

What GONAL-f contains

- The active substance is follitropin alfa.
- Each vial contains 5.5 micrograms of follitropin alfa.
- After preparation of the final solution for injection, there are 75 IU (5.5 micrograms) of follitropin alfa in each millilitre of solution.
- The other ingredients are sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, methionine, polysorbate 20, as well as concentrated phosphoric acid and sodium hydroxide for pH adjustment.
- The solvent is water for injections.

What GONAL-f looks like and contents of the pack

- GONAL-f is presented as a powder and solvent for solution which are used to prepare a solution for injection.
- The powder is a white pellet in a glass vial.
- The solvent is a clear colourless liquid in a pre-filled syringe, each containing 1 mL.
- GONAL-f is supplied in packs of 1, 5, 10 vials of powder with the corresponding number of solvent in pre-filled syringes. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Merck Europe B.V., Gustav Mahlerplein 102, 1082 MA Amsterdam, The Netherlands

Manufacturer

Merck Serono S.p.A., Via delle Magnolie 15, 70026 Modugno (Bari), Italy

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

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:

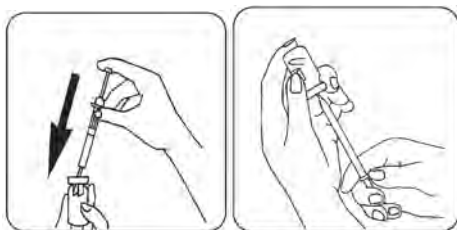
- 1 pre-filled syringe containing the solvent (the clear liquid)
- 1 vial containing GONAL-f (the white powder)
- 1 needle for preparation
- 1 fine bore needle for injection under the skin

Not provided in the pack:

- 2 alcohol swabs
- 1 sharps container

3. Preparing the solution

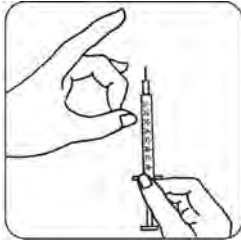
- Remove the protective caps from the powder vial and from the pre-filled syringe.
- Attach the needle for preparation to the pre-filled syringe, insert it into the powder vial and slowly inject all the solvent. Swirl gently without removing the syringe. Do not shake.
- Check that the resulting solution 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.)

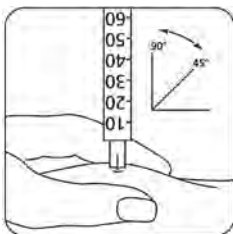
4. Getting ready the syringe for injection

- 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 sharps container. Any unused solution must be discarded.

Package leaflet: Information for the user

GONAL-f 1050 IU/1.75 mL powder and solvent for solution for injection follitropin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What GONAL-f is and what it is used for
2. What you need to know before you use GONAL-f
3. How to use GONAL-f
4. Possible side effects
5. How to store GONAL-f
6. Contents of the pack and other information
How to prepare and use the GONAL-f powder and solvent

1. What GONAL-f is and what it is used for

What GONAL-f is

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.

What GONAL-f is used for

In adult women, GONAL-f is used:

- to help release an egg from the ovary (ovulation) in women that cannot ovulate and that did not respond to treatment with a medicine called “clomiphene citrate”.
- together with another medicine called “lutropin alfa” (“luteinising hormone” or LH) to help release egg from the ovary (ovulation) in women whose body is producing very little gonadotropins (FSH and LH).
- to help develop several follicles (each containing an egg) in women undergoing assisted reproductive technology procedures (procedures that may help you to become pregnant) such as “*in vitro* fertilisation”, “gamete intra-fallopian transfer” or “zygote intra-fallopian transfer”.

In adult men, GONAL-f is used:

- together with another medicine called “human chorionic gonadotropin” (hCG) to help produce sperm in men that are infertile due to a low level of certain hormones.

2. What you need to know before you use GONAL-f

You and your partner’s fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility disorders.

Do not use GONAL-f

- if you are allergic to follicle stimulating hormone or any of the other ingredients of this medicine listed in section 6.
- if you have a tumour in your hypothalamus or pituitary gland (both are parts of the brain).
- if you are **a woman**:
 - with large ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
 - with unexplained vaginal bleeding.
 - with cancer in your ovaries, womb or breasts.
 - with a condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), or malformed reproductive organs.
- if you are **a man**:
 - with damaged testicles that cannot be healed.

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Gonal-f.

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).

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.

Ovarian hyper-stimulation syndrome (OHSS)

If you are a woman, this medicine increases your risk of developing OHSS. This is when your follicles develop too much and become large cysts. If you get lower abdominal pain, gain any weight rapidly, feel sick or are vomiting or if you have difficulty in breathing, talk to your doctor straight away who might ask you to stop using this medicine (see section 4).

In case you are not ovulating, and if the recommended dose and schedule of administration are adhered to, the occurrence of OHSS is less likely. GONAL-f treatment seldom causes severe OHSS unless the medicine that is used for final follicular maturation (containing human chorionic gonadotropin, 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.

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. When undergoing assisted reproductive technology, the risk of having a multiple pregnancy is related to your age, the quality and the number of fertilised eggs or embryos placed inside you.

Miscarriage

When undergoing assisted reproductive technology or stimulation of your ovaries to produce eggs, you are more likely to have a miscarriage than the average woman.

Blood clotting problems (thromboembolic events)

If you had in the past or recently blood clots in the leg or in the lung, or a heart attack or stroke, or if those happened in your family, then you might have a higher risk that these problems occur or become worse with GONAL-f treatment.

Men with too much FSH in their blood

If you are a man, having too much FSH in your blood can be a sign of damaged testicles. GONAL-f usually does not work if you have this problem.

If your doctor decides to try GONAL-f treatment, to monitor the treatment, they may ask you to provide semen for analysis 4 to 6 months after starting treatment.

Children and adolescents

GONAL-f is not for use in children and adolescents below 18 years old.

Other medicines and GONAL-f

Tell your doctor if you are taking, have recently taken or might take any other medicines.

- If you use GONAL-f with other medicines which help ovulation (such as hCG or clomiphene citrate), this may increase the response of your follicles.
- If you use GONAL-f at the same time as a “gonadotropin-releasing hormone” (GnRH) agonist or antagonist (these medicines reduce your sex hormone levels and stop you ovulating) you may need a higher dose of GONAL-f to produce follicles.

Pregnancy and breast-feeding

Do not use GONAL-f if you are pregnant or breast-feeding.

Driving and using machines

It is not expected that this medicine will affect your ability to drive and use machines.

GONAL-f contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially “sodium-free”.

When prepared with the solvent provided, this medicine contains 1.23 mg benzyl alcohol in each 75 IU dose which is equivalent to 9.45 mg/mL. Benzyl alcohol may cause allergic reactions.

3. How to use GONAL-f

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Using this medicine

- GONAL-f is intended to be given by injection just under the skin (subcutaneously). The prepared solution 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 inject GONAL-f before you can inject yourself.
- If you administer GONAL-f to yourself, please carefully read and follow the instructions at the end of this leaflet called “How to prepare and use the GONAL-f powder and solution”.

How much to use

Your doctor will decide how much medicine you will take and how often. The doses described below are stated in International Units (IU), which reflects the grading of the administration syringes provided in the pack.

If you use another syringe, which shows millilitres (mL) instead of IUs, you can take the correct amount for injection in mL from the following table:

Dose to be injected (IU)	Volume to be injected (mL)
75	0.13
150	0.25
225	0.38
300	0.50
375	0.63
450	0.75

Women

If you are not ovulating and have irregular or no periods.

- GONAL-f is usually given every day.
- If you have irregular periods, start using GONAL-f within the first 7 days of your menstrual cycle. If you do not have periods you can start using the medicine on any convenient day.
- The usual starting dose of GONAL-f is 75 to 150 IU each day.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- The maximum daily dose of GONAL-f is usually not higher than 225 IU.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last GONAL-f injection. The best time to have sex is on the day of the hCG injection and the day after.

If your doctor cannot see a desired response after 4 weeks, that treatment cycle with GONAL-f should be stopped. For the following treatment cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you have been diagnosed with very low levels of FSH and LH hormones

- The usual starting dose of GONAL-f is 75 to 150 IU together with 75 IU of lutropin alfa.
- You will use these two medicines each day for up to five weeks.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last injections of GONAL-f and lutropin alfa. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on your doctor’s judgment.

If your doctor cannot see a response after 5 weeks, that treatment cycle with GONAL-f should be stopped. For the following cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment with GONAL-f will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you need to develop several eggs for collection prior to any assisted reproductive technology

- The usual starting dose of GONAL-f is 150 to 225 IU each day, from day 2 or 3 of your treatment cycle.
- GONAL-f dose may be increased, depending on your response. The maximum daily dose is 450 IU.
- Treatment is continued until your eggs have developed to a desired point. This usually takes about 10 days but can take any time between 5 and 20 days. Your doctor will use blood tests and/or an ultrasound machine to check when this is.
- When your eggs are ready, you will be given a single injection of 250 micrograms “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special recombinant DNA technique), or 5 000 IU to 10 000 IU of hCG, 24 to 48 hours after the last GONAL-f injection. This gets your eggs ready for collection.

In other cases, your doctor may first stop you from ovulating by using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Then GONAL-f is started approximately two weeks after start of agonist treatment. The GONAL-f and GnRH agonist are then both given until your follicles develop as desired. For example, after two weeks of GnRH agonist treatment, 150 to 225 IU GONAL-f is administered for 7 days. The dose is then adjusted according to your ovarian response.

Men

- The usual dose of GONAL-f is 150 IU together with hCG.
- You will use these two medicines three times a week for at least 4 months.
- If you have not responded to treatment after 4 months, your doctor may suggest that you continue using these two medicines for at least 18 months.

If you use more GONAL-f than you should

The effects of taking too much GONAL-f are unknown. Nevertheless, one could expect ovarian hyper-stimulation syndrome (OHSS) to occur, which is described in section 4. However, the OHSS will only occur if hCG is also administered (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”).

If you forget to use GONAL-f

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.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects in women

- Lower abdominal pain together with nausea or vomiting may be the symptoms of ovarian hyper-stimulation syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed (see also in section 2. under “Ovarian hyper-stimulation syndrome (OHSS)”). This side effect is common (may affect up to 1 in 10 people).
- 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 side effect is uncommon (may affect up to 1 in 100 people).
- Complications of OHSS such as twisting of ovaries or blood clotting may occur rarely (may affect up to 1 in 1 000 people).
- Serious blood clotting complications (thromboembolic events) sometimes independent of OHSS may be found very rarely (may affect up to 1 in 10 000 people). This could cause chest pain, breathlessness, stroke or heart attack (see also in section 2. under “Blood clotting problems”).

Serious side effects in men and women

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing can sometimes be serious. This side effect is very rare (may affect up to 1 in 10 000 people).

If you notice any of the above-listed side effects, you should immediately contact your doctor who might ask you to stop using GONAL-f.

Other side effects in women

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

- Abdominal pain
- Feeling sick, vomiting, diarrhoea, abdominal cramps and bloating

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Other side effects in men

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

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

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty in breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GONAL-f

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label or carton after EXP. The expiry date refers to the last day of that month.

Prior to reconstitution, 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.

Once the solution has been prepared, it may be stored for a maximum of 28 days.

- Please write on the GONAL-f vial the day you prepared the solution.
- Do not store above 25°C. Do not freeze.
- Store in the original container, in order to protect from light.
- Do not use any GONAL-f solution left in the vial after 28 days.

At the end of the treatment any unused solution must be discarded.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

GONAL-f 1050 IU/1.75 mL powder should not be mixed with other medicines in the same injection. GONAL-f 1050 IU/1.75 mL powder is not to be mixed with other GONAL-f containers within the same vial or syringe.

6. Contents of the pack and other information

What GONAL-f contains

- The active substance is follitropin alfa.
- Each vial contains 1 200 IU of follitropin alfa.
- After reconstitution, there are 1 050 IU (77 micrograms) of follitropin alfa in 1.75 mL solution, that means there are 600 IU (44 micrograms) in each millilitre of solution.
- The other ingredients are sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, as well as concentrated phosphoric acid and sodium hydroxide for pH adjustment.
- The solvent contains water for injections and benzyl alcohol.

What GONAL-f looks like and contents of the pack

- GONAL-f is presented as a powder and solvent which are used to prepare a solution for injection.
- The powder is a white pellet in a multidose glass vial.
- The solvent is a clear colourless liquid in a pre-filled syringe, each containing 2 mL.
- GONAL-f is supplied in packs of 1 vial of powder with 1 pre-filled syringe of solvent and 15 disposable syringes for administration graduated in International Units (IU FSH).

Marketing Authorisation Holder

Merck Europe B.V., Gustav Mahlerplein 102, 1082 MA Amsterdam, The Netherlands

Manufacturer

Merck Serono S.p.A., Via delle Magnolie 15, 70026 Modugno (Bari), Italy

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

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

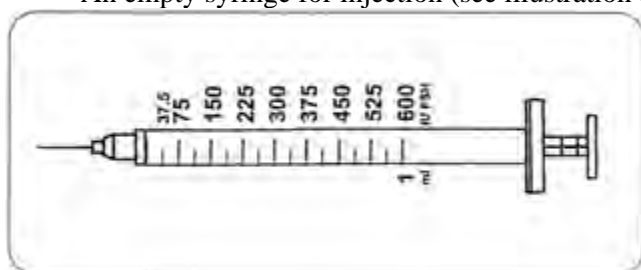
- This section tells you how to prepare and use your GONAL-f powder and solvent.
- Before starting the preparation, please read these instructions the whole way through first.
- Give yourself the injection at the same time each day.

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:

- 2 alcohol swabs
- The pre-filled syringe containing the solvent (the clear liquid)
- The vial containing GONAL-f (the white powder)
- An empty syringe for injection (see illustration below)



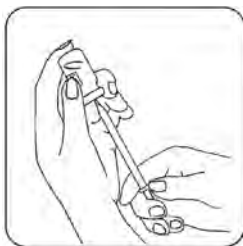
3. Preparing the solution

- Remove the protective caps from the powder vial and from the pre-filled syringe.
- Take your pre-filled syringe, insert the needle into the powder vial and slowly inject all the solvent into the vial containing the powder.
- Remove the syringe from the vial and throw it away (put the protective cap to avoid injuries).
- This vial contains several doses of GONAL-f. You will have to keep it several days and only draw the prescribed dose every day.



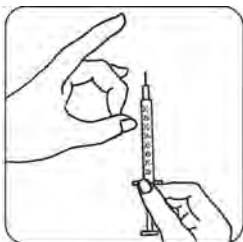
4. Getting ready the syringe for injection

- Swirl gently the vial of GONAL-f prepared in step 3, do not shake. Check that the solution is clear and does not contain any particles.
- Take the syringe for injection and fill it with air by pulling the plunger to the correct dose in International Units (IU FSH).
- Insert the needle into the vial, turn the vial upside down and inject the air into the vial.
- Draw the prescribed dose of GONAL-f into the syringe for administration by pulling the plunger until it reaches the correct dose in IU FSH.



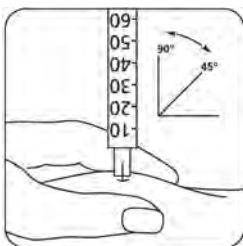
5. Removing air bubbles

- 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.



6. 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.



7. After the injection

- Once you have finished your injection, immediately discard the used syringes safely, preferably in a sharps container.
- Store the glass vial with the prepared solution in a safe place. You may need it again. The prepared solution is for your use alone and must not be given to other patients.
- For further injections with the prepared solution of GONAL-f, repeat steps 4 to 7.

Package leaflet: Information for the user

GONAL-f 450 IU/0.75 mL powder and solvent for solution for injection follitropin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What GONAL-f is and what it is used for
2. What you need to know before you use GONAL-f
3. How to use GONAL-f
4. Possible side effects
5. How to store GONAL-f
6. Contents of the pack and other information
How to prepare and use the GONAL-f powder and solvent

1. What GONAL-f is and what it is used for

What GONAL-f is

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.

What GONAL-f is used for

In adult women, GONAL-f is used:

- to help release an egg from the ovary (ovulation) in women that cannot ovulate and that did not respond to treatment with a medicine called “clomiphene citrate”.
- together with another medicine called “lutropin alfa” (“luteinising hormone” or LH) to help release egg from the ovary (ovulation) in women whose body is producing very little gonadotropins (FSH and LH).
- to help develop several follicles (each containing an egg) in women undergoing assisted reproductive technology procedures (procedures that may help you to become pregnant) such as “*in vitro* fertilisation”, “gamete intra-fallopian transfer” or “zygote intra-fallopian transfer”.

In adult men, GONAL-f is used:

- together with another medicine called “human chorionic gonadotropin” (hCG) to help produce sperm in men that are infertile due to a low level of certain hormones.

2. What you need to know before you use GONAL-f

You and your partner’s fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility disorders.

Do not use GONAL-f

- if you are allergic to follicle stimulating hormone or any of the other ingredients of this medicine listed in section 6.
- if you have a tumour in your hypothalamus or pituitary gland (both are parts of the brain).
- if you are **a woman**:
 - with large ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
 - with unexplained vaginal bleeding.
 - with cancer in your ovaries, womb or breasts.
 - with a condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), or malformed reproductive organs.
- if you are **a man**:
 - with damaged testicles that cannot be healed.

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Gonal-f.

Porphyrria

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).

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.

Ovarian hyper-stimulation syndrome (OHSS)

If you are a woman, this medicine increases your risk of developing OHSS. This is when your follicles develop too much and become large cysts. If you get lower abdominal pain, gain any weight rapidly, feel sick or are vomiting or if you have difficulty in breathing, talk to your doctor straight away who might ask you to stop using this medicine (see section 4).

In case you are not ovulating, and if the recommended dose and schedule of administration are adhered to, the occurrence of OHSS is less likely. GONAL-f treatment seldom causes severe OHSS unless the medicine that is used for final follicular maturation (containing human chorionic gonadotropin, 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.

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. When undergoing assisted reproductive technology, the risk of having a multiple pregnancy is related to your age, the quality and the number of fertilised eggs or embryos placed inside you.

Miscarriage

When undergoing assisted reproductive technology or stimulation of your ovaries to produce eggs, you are more likely to have a miscarriage than the average woman.

Blood clotting problems (thromboembolic events)

If you had in the past or recently blood clots in the leg or in the lung, or a heart attack or stroke, or if those happened in your family, then you might have a higher risk that these problems occur or become worse with GONAL-f treatment.

Men with too much FSH in their blood

If you are a man, having too much FSH in your blood can be a sign of damaged testicles. GONAL-f usually does not work if you have this problem.

If your doctor decides to try GONAL-f treatment, to monitor the treatment, they may ask you to provide semen for analysis 4 to 6 months after starting treatment.

Children and adolescents

GONAL-f is not for use in children and adolescents below 18 years old.

Other medicines and GONAL-f

Tell your doctor if you are taking, have recently taken or might take any other medicines.

- If you use GONAL-f with other medicines which help ovulation (such as hCG or clomiphene citrate), this may increase the response of your follicles.
- If you use GONAL-f at the same time as a “gonadotropin-releasing hormone” (GnRH) agonist or antagonist (these medicines reduce your sex hormone levels and stop you ovulating) you may need a higher dose of GONAL-f to produce follicles.

Pregnancy and breast-feeding

Do not use GONAL-f if you are pregnant or breast-feeding.

Driving and using machines

It is not expected that this medicine will affect your ability to drive and use machines.

GONAL-f contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially “sodium-free”.

When prepared with the solvent provided, this medicine contains 1.23 mg benzyl alcohol in each 75 IU dose which is equivalent to 9.45 mg/mL. Benzyl alcohol may cause allergic reactions.

3. How to use GONAL-f

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Using this medicine

- GONAL-f is intended to be given by injection just under the skin (subcutaneously). The prepared solution 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 inject GONAL-f before you can inject yourself.
- If you administer GONAL-f to yourself, please carefully read and follow the instructions at the end of this leaflet called “How to prepare and use the GONAL-f powder and solution”.

How much to use

Your doctor will decide how much medicine you will take and how often. The doses described below are stated in International Units (IU), which reflects the grading of the administration syringes provided in the pack.

If you use another syringe, which shows millilitres (mL) instead of IUs, you can take the correct amount for injection in mL from the following table:

Dose to be injected (IU)	Volume to be injected (mL)
75	0.13
150	0.25
225	0.38
300	0.50
375	0.63
450	0.75

Women

If you are not ovulating and have irregular or no periods.

- GONAL-f is usually given every day.
- If you have irregular periods, start using GONAL-f within the first 7 days of your menstrual cycle. If you do not have periods you can start using the medicine on any convenient day.
- The usual starting dose of GONAL-f is 75 to 150 IU each day.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- The maximum daily dose of GONAL-f is usually not higher than 225 IU.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last GONAL-f injection. The best time to have sex is on the day of the hCG injection and the day after.

If your doctor cannot see a desired response after 4 weeks, that treatment cycle with GONAL-f should be stopped. For the following treatment cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you have been diagnosed with very low levels of FSH and LH hormones

- The usual starting dose of GONAL-f is 75 to 150 IU together with 75 IU of lutropin alfa.
- You will use these two medicines each day for up to five weeks.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last injections of GONAL-f and lutropin alfa. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on your doctor’s judgment.

If your doctor cannot see a response after 5 weeks, that treatment cycle with GONAL-f should be stopped. For the following cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment with GONAL-f will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you need to develop several eggs for collection prior to any assisted reproductive technology

- The usual starting dose of GONAL-f is 150 to 225 IU each day, from day 2 or 3 of your treatment cycle.
- GONAL-f dose may be increased, depending on your response. The maximum daily dose is 450 IU.
- Treatment is continued until your eggs have developed to a desired point. This usually takes about 10 days but can take any time between 5 and 20 days. Your doctor will use blood tests and/or an ultrasound machine to check when this is.
- When your eggs are ready, you will be given a single injection of 250 micrograms “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special recombinant DNA technique), or 5 000 IU to 10 000 IU of hCG, 24 to 48 hours after the last GONAL-f injection. This gets your eggs ready for collection.

In other cases, your doctor may first stop you from ovulating by using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Then GONAL-f is started approximately two weeks after start of agonist treatment. The GONAL-f and GnRH agonist are then both given until your follicles develop as desired. For example, after two weeks of GnRH agonist treatment, 150 to 225 IU GONAL-f is administered for 7 days. The dose is then adjusted according to your ovarian response.

Men

- The usual dose of GONAL-f is 150 IU together with hCG.
- You will use these two medicines three times a week for at least 4 months.
- If you have not responded to treatment after 4 months, your doctor may suggest that you continue using these two medicines for at least 18 months.

If you use more GONAL-f than you should

The effects of taking too much GONAL-f are unknown. Nevertheless, one could expect ovarian hyper-stimulation syndrome (OHSS) to occur, which is described in section 4. However, the OHSS will only occur if hCG is also administered (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”).

If you forget to use GONAL-f

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.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects in women

- Lower abdominal pain together with nausea or vomiting may be the symptoms of ovarian hyper-stimulation syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed (see also in section 2. under “Ovarian hyper-stimulation syndrome (OHSS)”). This side effect is common (may affect up to 1 in 10 people).
- 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 side effect is uncommon (may affect up to 1 in 100 people).
- Complications of OHSS such as twisting of ovaries or blood clotting may occur rarely (may affect up to 1 in 1 000 people).
- Serious blood clotting complications (thromboembolic events) sometimes independent of OHSS may be found very rarely (may affect up to 1 in 10 000 people). This could cause chest pain, breathlessness, stroke or heart attack (see also in section 2. under “Blood clotting problems”).

Serious side effects in men and women

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing can sometimes be serious. This side effect is very rare (may affect up to 1 in 10 000 people).

If you notice any of the above-listed side effects, you should immediately contact your doctor who might ask you to stop using GONAL-f.

Other side effects in women

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

- Abdominal pain
- Feeling sick, vomiting, diarrhoea, abdominal cramps and bloating

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Other side effects in men

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

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

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty in breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GONAL-f

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label or carton after EXP. The expiry date refers to the last day of that month.

Prior to reconstitution, 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.

Once the solution has been prepared, it may be stored for a maximum of 28 days.

- Please write on the GONAL-f vial the day you prepared the solution.
- Do not store above 25°C. Do not freeze.
- Store in the original container, in order to protect from light.
- Do not use any GONAL-f solution left in the vial after 28 days.

At the end of the treatment any unused solution must be discarded.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

GONAL-f 450 IU/0.75 mL powder should not be mixed with other medicines in the same injection. GONAL-f 450 IU/0.75 mL powder is not to be mixed with other GONAL-f containers within the same vial or syringe.

6. Contents of the pack and other information

What GONAL-f contains

- The active substance is follitropin alfa.
- Each vial contains 600 IU of follitropin alfa.
- After reconstitution, there are 450 IU (33 micrograms) of follitropin alfa in 0.75 mL solution, that means there are 600 IU (44 micrograms) in each millilitre of solution.
- The other ingredients are sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, as well as concentrated phosphoric acid and sodium hydroxide for pH adjustment.
- The solvent contains water for injections and benzyl alcohol.

What GONAL-f looks like and contents of the pack

- GONAL-f is presented as a powder and solvent which are used to prepare a solution for injection.
- The powder is a white pellet in a multidose glass vial.
- The solvent is a clear colourless liquid in a pre-filled syringe, each containing 1 mL.
- GONAL-f is supplied in packs of 1 vial of powder with 1 pre-filled syringe of solvent and 6 disposable syringes for administration graduated in International Units (IU FSH).

Marketing Authorisation Holder

Merck Europe B.V., Gustav Mahlerplein 102, 1082 MA Amsterdam, The Netherlands

Manufacturer

Merck Serono S.p.A., Via delle Magnolie 15, 70026 Modugno (Bari), Italy

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

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

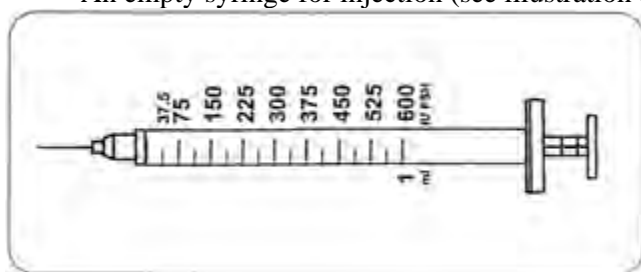
- This section tells you how to prepare and use your GONAL-f powder and solvent.
- Before starting the preparation, please read these instructions the whole way through first.
- Give yourself the injection at the same time each day.

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:

- 2 alcohol swabs
- The pre-filled syringe containing the solvent (the clear liquid)
- The vial containing GONAL-f (the white powder)
- An empty syringe for injection (see illustration below)



3. Preparing the solution

- Remove the protective caps from the powder vial and from the pre-filled syringe.
- Take your pre-filled syringe, insert the needle into the powder vial and slowly inject all the solvent into the vial containing the powder.
- Remove the syringe from the vial and throw it away (put the protective cap to avoid injuries).
- This vial contains several doses of GONAL-f. You will have to keep it several days and only draw the prescribed dose every day.



4. Getting ready the syringe for injection

- Swirl gently the vial of GONAL-f prepared in step 3, do not shake. Check that the solution is clear and does not contain any particles.
- Take the syringe for injection and fill it with air by pulling the plunger to the correct dose in International Units (IU FSH).
- Insert the needle into the vial, turn the vial upside down and inject the air into the vial.
- Draw the prescribed dose of GONAL-f into the syringe for administration by pulling the plunger until it reaches the correct dose in IU FSH.



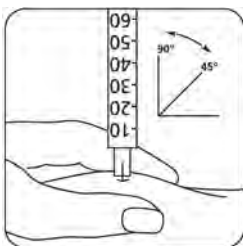
5. Removing air bubbles

- 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.



6. 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.



7. After the injection

- Once you have finished your injection, immediately discard the used syringes safely, preferably in a sharps container.
- Store the glass vial with the prepared solution in a safe place. You may need it again. The prepared solution is for your use alone and must not be given to other patients.
- For further injections with the prepared solution of GONAL-f, repeat steps 4 to 7.

Package leaflet: Information for the user

GONAL-f 150 IU/0.24 mL solution for injection in pre-filled pen follitropin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What GONAL-f is and what it is used for
 2. What you need to know before you use GONAL-f
 3. How to use GONAL-f
 4. Possible side effects
 5. How to store GONAL-f
 6. Contents of the pack and other information
- Instructions for use

1. What GONAL-f is and what it is used for

What GONAL-f is

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In adult women, GONAL-f is used:

- to help release an egg from the ovary (ovulation) in women that cannot ovulate and that did not respond to treatment with a medicine called “clomiphene citrate”.
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- to help develop several follicles (each containing an egg) in women undergoing assisted reproductive technology procedures (procedures that may help you to become pregnant) such as “*in vitro* fertilisation”, “gamete intra-fallopian transfer” or “zygote intra-fallopian transfer”.

In adult men, GONAL-f is used:

- together with another medicine called “human chorionic gonadotropin” (hCG) to help produce sperm in men that are infertile due to a low level of certain hormones.

2. What you need to know before you use GONAL-f

You and your partner’s fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility disorders.

Do not use GONAL-f

- if you are allergic to follicle stimulating hormone or any of the other ingredients of this medicine listed in section 6.
- if you have a tumour in your hypothalamus or pituitary gland (both are parts of the brain).
- if you are **a woman**:
 - with large ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
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 - with cancer in your ovaries, womb or breasts.
 - with a condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), or malformed reproductive organs.
- if you are **a man**:
 - with damaged testicles that cannot be healed.

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Gonal-f.

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).

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.

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If you are a woman, this medicine increases your risk of developing OHSS. This is when your follicles develop too much and become large cysts. If you get lower abdominal pain, gain any weight rapidly, feel sick or are vomiting or if you have difficulty in breathing, talk to your doctor straight away who might ask you to stop using this medicine (see section 4).

In case you are not ovulating, and if the recommended dose and schedule of administration are adhered to, the occurrence of OHSS is less likely. GONAL-f treatment seldom causes severe OHSS unless the medicine that is used for final follicular maturation (containing human chorionic gonadotropin, 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.

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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. When undergoing assisted reproductive technology, the risk of having a multiple pregnancy is related to your age, the quality and the number of fertilised eggs or embryos placed inside you.

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When undergoing assisted reproductive technology or stimulation of your ovaries to produce eggs, you are more likely to have a miscarriage than the average woman.

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If you had in the past or recently blood clots in the leg or in the lung, or a heart attack or stroke, or if those happened in your family, then you might have a higher risk that these problems occur or become worse with GONAL-f treatment.

Men with too much FSH in their blood

If you are a man, having too much FSH in your blood can be a sign of damaged testicles. GONAL-f usually does not work if you have this problem.

If your doctor decides to try GONAL-f treatment, to monitor the treatment, they may ask you to provide semen for analysis 4 to 6 months after starting treatment.

Children and adolescents

GONAL-f is not for use in children and adolescents below 18 years old.

Other medicines and GONAL-f

Tell your doctor if you are taking, have recently taken or might take any other medicines.

- If you use GONAL-f with other medicines which help ovulation (such as hCG or clomiphene citrate), this may increase the response of your follicles.
- If you use GONAL-f at the same time as a “gonadotropin-releasing hormone” (GnRH) agonist or antagonist (these medicines reduce your sex hormone levels and stop you ovulating) you may need a higher dose of GONAL-f to produce follicles.

Pregnancy and breast-feeding

Do not use GONAL-f if you are pregnant or breast-feeding.

Driving and using machines

It is not expected that this medicine will affect your ability to drive and use machines.

GONAL-f contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially “sodium-free”.

3. How to use GONAL-f

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Using this medicine

- GONAL-f is intended to be given by injection just under the skin (subcutaneously). 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.
- If you administer GONAL-f to yourself, please carefully read and follow the “Instructions for use”.

How much to use

Your doctor will decide how much medicine you will take and how often. The doses described below are stated in International Units (IU).

Women

If you are not ovulating and have irregular or no periods.

- GONAL-f is usually given every day.
- If you have irregular periods, start using GONAL-f within the first 7 days of your menstrual cycle. If you do not have periods you can start using the medicine on any convenient day.
- The usual starting dose of GONAL-f is 75 to 150 IU each day.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- The maximum daily dose of GONAL-f is usually not higher than 225 IU.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last GONAL-f injection. The best time to have sex is on the day of the hCG injection and the day after.

If your doctor cannot see a desired response after 4 weeks, that treatment cycle with GONAL-f should be stopped. For the following treatment cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you have been diagnosed with very low levels of FSH and LH hormones

- The usual starting dose of GONAL-f is 75 to 150 IU together with 75 IU of lutropin alfa.
- You will use these two medicines each day for up to five weeks.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last injections of GONAL-f and lutropin alfa. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on your doctor’s judgment.

If your doctor cannot see a response after 5 weeks, that treatment cycle with GONAL-f should be stopped. For the following cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment with GONAL-f will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you need to develop several eggs for collection prior to any assisted reproductive technology

- The usual starting dose of GONAL-f is 150 to 225 IU each day, from day 2 or 3 of your treatment cycle.
- GONAL-f dose may be increased, depending on your response. The maximum daily dose is 450 IU.
- Treatment is continued until your eggs have developed to a desired point. This usually takes about 10 days but can take any time between 5 and 20 days. Your doctor will use blood tests and/or an ultrasound machine to check when this is.
- When your eggs are ready, you will be given a single injection of 250 micrograms “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special recombinant DNA technique), or 5 000 IU to 10 000 IU of hCG, 24 to 48 hours after the last GONAL-f injection. This gets your eggs ready for collection.

In other cases, your doctor may first stop you from ovulating by using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Then GONAL-f is started approximately two weeks after start of agonist treatment. The GONAL-f and GnRH agonist are then both given until your follicles develop as desired. For example, after two weeks of GnRH agonist treatment, 150 to 225 IU GONAL-f is administered for 7 days. The dose is then adjusted according to your ovarian response.

Men

- The usual dose of GONAL-f is 150 IU together with hCG.
- You will use these two medicines three times a week for at least 4 months.
- If you have not responded to treatment after 4 months, your doctor may suggest that you continue using these two medicines for at least 18 months.

If you use more GONAL-f than you should

The effects of taking too much GONAL-f are unknown. Nevertheless, one could expect ovarian hyper-stimulation syndrome (OHSS) to occur, which is described in section 4. However, the OHSS will only occur if hCG is also administered (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”).

If you forget to use GONAL-f

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.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects in women

- Lower abdominal pain together with nausea or vomiting may be the symptoms of ovarian hyper-stimulation syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed (see also in section 2. under “Ovarian hyper-stimulation syndrome (OHSS)”). This side effect is common (may affect up to 1 in 10 people).
- 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 side effect is uncommon (may affect up to 1 in 100 people).
- Complications of OHSS such as twisting of ovaries or blood clotting may occur rarely (may affect up to 1 in 1 000 people).
- Serious blood clotting complications (thromboembolic events) sometimes independent of OHSS may be found very rarely (may affect up to 1 in 10 000 people). This could cause chest pain, breathlessness, stroke or heart attack (see also in section 2. under “Blood clotting problems”).

Serious side effects in men and women

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing can sometimes be serious. This side effect is very rare (may affect up to 1 in 10 000 people).

If you notice any of the above-listed side effects, you should immediately contact your doctor who might ask you to stop using GONAL-f.

Other side effects in women

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

- Abdominal pain
- Feeling sick, vomiting, diarrhoea, abdominal cramps and bloating

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Other side effects in men

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

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

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty in breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GONAL-f

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the cartridge label or carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Before opening and within its shelf life, the product may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months and must be discarded if it has not been used within these 3 months.

Keep the cap on the pen, 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.

Please write on the GONAL-f pre-filled pen the day you first use it. For this purpose, a sticker is provided with the “Instructions for use”.

- Once opened, the pen should be stored between 2°C and 25°C for a maximum of 28 days.
- 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 throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What GONAL-f contains

- The active substance is follitropin alfa.
- Each pre-filled pen with multidose cartridge contains 150 IU (11 micrograms) of follitropin alfa in 0.24 mL solution.
- The other ingredients are poloxamer 188, sucrose, methionine, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, m-cresol, as well as concentrated phosphoric acid and sodium hydroxide for pH adjustment and water for injections.

What GONAL-f looks like and contents of the pack

- GONAL-f is presented as a clear, colourless liquid for injection in a pre-filled pen.
- It is supplied in packs with 1 pre-filled pen and 4 disposable needles.

Marketing Authorisation Holder

Merck Europe B.V., Gustav Mahlerplein 102, 1082 MA Amsterdam, The Netherlands

Manufacturer

Merck Serono S.p.A., Via delle Magnolie 15, 70026 Modugno (Bari), Italy

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

Instructions for use

GONAL-f PRE-FILLED PEN 150 IU/0.24 mL Solution for injection in pre-filled pen Follitropin alfa

Table of Contents

Important information about the GONAL-f pre-filled pen
How to use your GONAL-f pre-filled pen treatment diary
Get familiar with your GONAL-f pre-filled pen
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Step 2 Get ready for injection
Step 3 Attach your needle
Step 4 Dial your dose
Step 5 Inject your dose
Step 6 Remove the needle after each injection
Step 7 After the injection
Step 8 Store the GONAL-f pre-filled pen
GONAL-f pre-filled pen treatment diary

Important information about the GONAL-f pre-filled pen

- Read the Instructions for Use and the Package Leaflet before using your GONAL-f pre-filled pen.
- Always follow all directions in this Instructions for Use and training provided by your healthcare provider as they may differ from your past experience. This information will allow to prevent incorrect treatment or infection by needle stick or broken glass injury.
- The GONAL-f pre-filled pen is for subcutaneous injection only.
- Only use the GONAL-f pre-filled pen if your healthcare provider trains you on how to use it correctly.
- Your healthcare provider will tell you how many GONAL-f pre-filled pens you need to complete your treatment.
- Give yourself the injection at the same time each day.
- The numbers in the **Dose Feedback Window** represent the number of International Units, or IUs, and show the dose of follitropin alfa. Your healthcare provider will tell you how many IUs of follitropin alfa to inject each day.
- The numbers displayed in the **Dose Feedback Window** help you to:

- a. Dial your prescribed dose (Figure 1).



Fig. 1

- b. Verify a complete injection (Figure 2).



Fig. 2

- c. Read the dose remaining to be injected with a second pen (Figure 3).



Fig. 3

- Remove the needle from the pen immediately after each injection.

Do not reuse needles.

Do not share the pen and/or needles with another person.

Do not use the GONAL-f pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

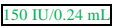

How to use your GONAL-f pre-filled pen treatment diary

A treatment diary is included on the last page. Use the treatment diary to record the amount injected. Injecting an incorrect amount of medicine could affect your treatment.

- Record the treatment day number (column 1), date (column 2), time of your injection (column 3), and volume of your pen (column 4).
- Record your prescribed dose (column 5).
- Check you dial the right dose before injecting (column 6).
- After injection, read the number shown in the **Dose Feedback Window**.
- Confirm you receive a complete injection (column 7) or record the number shown in the **Dose Feedback Window** if other than “0” (column 8).
- When needed, inject yourself using a second pen, dialing your remaining dose written in the “Amount to Be Set for a Second Injection” section (column 8).
- Record this remaining dose in the “**Amount Set to Inject**” section (column 6) in the next row.

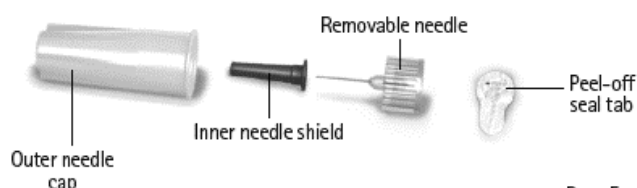
Using your treatment diary to record your daily injection(s) allows you to verify every day that you received the full prescribed dose.

An example of a treatment diary:

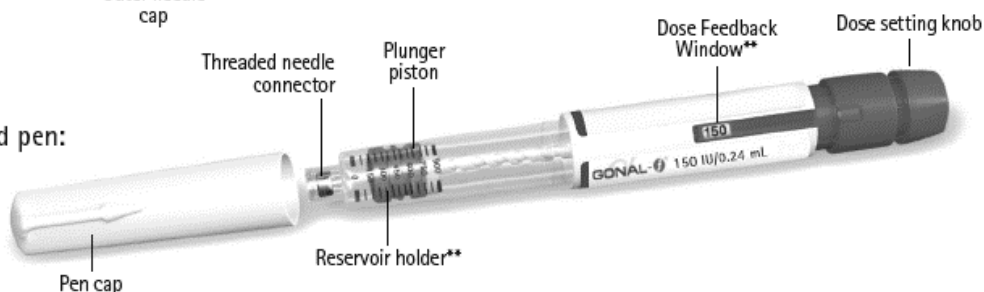
1 Treatment Day Number	2 Date	3 Time	4 Pen Volume 	5 Prescribed Dose	6 7 8		
					Dose Feedback Window		
					Amount Set to Inject	Amount to Be Set for a Second Injection 	
#1	10/06	07:00	150 IU	100	100	<input checked="" type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
#2	11/06/	07:00	150 IU	100	100	<input type="checkbox"/> if "0", injection complete	<input checked="" type="checkbox"/> if not "0", need second injection Inject this amount 50 using new pen
#2	11/06	07:00	150 IU	N/A	50	<input checked="" type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen

Get familiar with your GONAL-f pre-filled pen

Your needle*:



Your pre-filled pen:



*For illustrations purposes only.

**The numbers in the Dose Feedback Window and reservoir holder represent the number of International Units (IU) of medicine.

Step 1 Gather your supplies

- 1.1 Let the pre-filled pen sit at room temperature for at least 30 minutes before use to allow the medicine to reach room temperature.

Do not use a microwave or other heating element to warm up the pen.

- 1.2 Prepare a clean area and a flat surface, such as a table or countertop, in a well-lit area.

- 1.3 You will also need (not included in the pack):

- Alcohol swabs and a sharps container (Figure 4).

- 1.4 Wash your hands with soap and water and dry them well (Figure 5).

- 1.5 Use your hand to remove the GONAL-f pre-filled pen from the pack.

Do not use any tools, using tools might damage the pen.

- 1.6 Check the name on the pre-filled pen says GONAL-f.

- 1.7 Check the expiration date on the pen label (Figure 6).

Do not use the GONAL-f pre-filled pen if the expiration date has passed or if your pre-filled pen does not say GONAL-f.



Fig. 4



Fig. 5



Fig. 6

Step 2 Get ready for injection

- 2.1 Pull-off the pen cap (Figure 7).

- 2.2 Check that medicine is clear, colourless and does not contain particles.

Do not use the pre-filled pen if the medicine is discolored or cloudy, as this can cause an infection.

- 2.3 Check that the Dose Feedback Window is set to "0" (Figure 8).

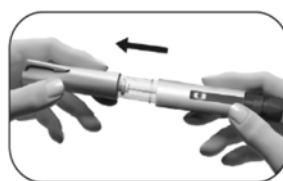


Fig. 7

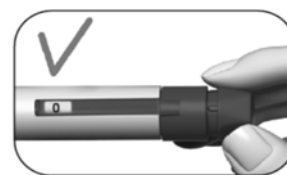


Fig. 8

Choose your injection site:

2.4 Your healthcare provider should show you the injection sites to use around your stomach area (Figure 9). To minimise skin irritation, select a different injection site each day.

2.5 Clean the skin at the injection site by wiping with an alcohol swab.

Do not touch or cover the cleaned skin.

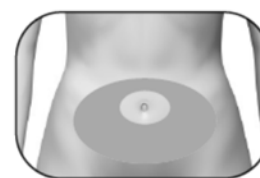


Fig. 9

Step 3 Attach your needle

Important: Always make sure to use a new needle for each injection. Re-using needles can cause infection.

3.1 Get a new needle. Only use the “single-use” needles supplied.

3.2 Check that the outer needle cap is not damaged.

3.3 Hold the outer needle cap firmly.

3.4 Check that the peel-off seal on the outer needle cap is not damaged or loose, and that expiration date has not passed (Figure 10).

3.5 Remove the peel-off seal (Figure 11).

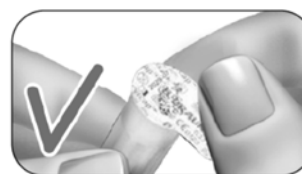


Fig. 10



Fig. 11

Do not use the needle if it is damaged, expired or if the outer needle cap or the peel-off seal is damaged or loose. Using expired needles or needles with damaged peel-off seal or outer needle cap can lead to infection. Throw it away in a sharps container and get a new needle.

3.6 Screw the outer needle cap onto the threaded tip of the GONAL-f pre-filled pen until you feel a light resistance (Figure 12).

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

3.7 Remove the outer needle cap by pulling it gently (Figure 13).

3.8 Put it aside for later use (Figure 14).

Do not discard the outer needle cap, as it will prevent needle stick injury and infection when detaching the needle from the pre-filled pen.

3.9 Hold the GONAL-f pre-filled pen with the needle pointing upward (Figure 15).

3.10 Carefully remove and discard the green inner needle shield (Figure 16).

Do not recap the needle with the green inner needle shield, as it can lead to needle stick injury and infection.

3.11 Look closely at the tip of the needle for tiny droplet(s) of liquid.

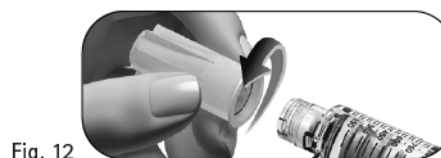


Fig. 12



Fig. 13



Fig. 14

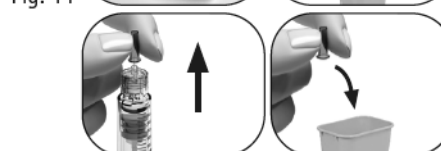


Fig. 15



Fig. 16

If	Then
Using a new pen	Check for a droplet of liquid at the tip of the needle (Figure 17). <ul style="list-style-type: none"> • If you see a tiny droplet of liquid, proceed to Step 4 Dial your dose. • If you do not see a tiny droplet at or near the needle tip, you must perform the steps on the next page to remove air in the system.
Reusing a pen	It is NOT required to check for a droplet of liquid. Proceed directly to Step 4 Dial your dose.

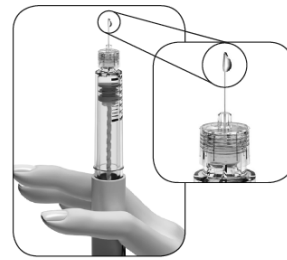


Fig. 17

If you do not see a tiny droplet(s) of liquid at or near the tip the first time you use a new pen:

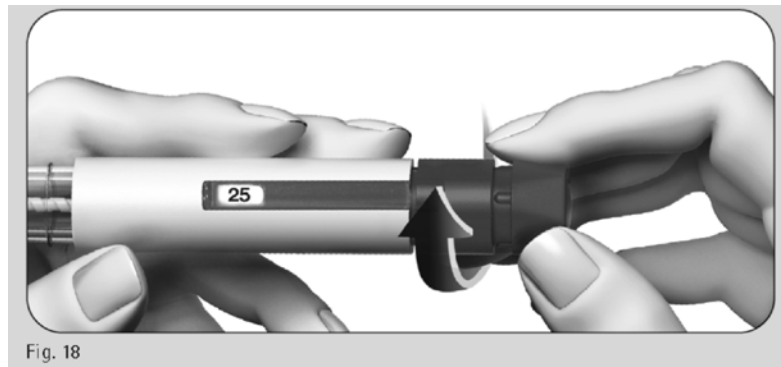


Fig. 18

1. Gently turn the dose setting knob forward until it **reads “25”** in the **Dose Feedback Window** (Figure 18).
 - You can turn the dose knob backward if you turn it past “25”.

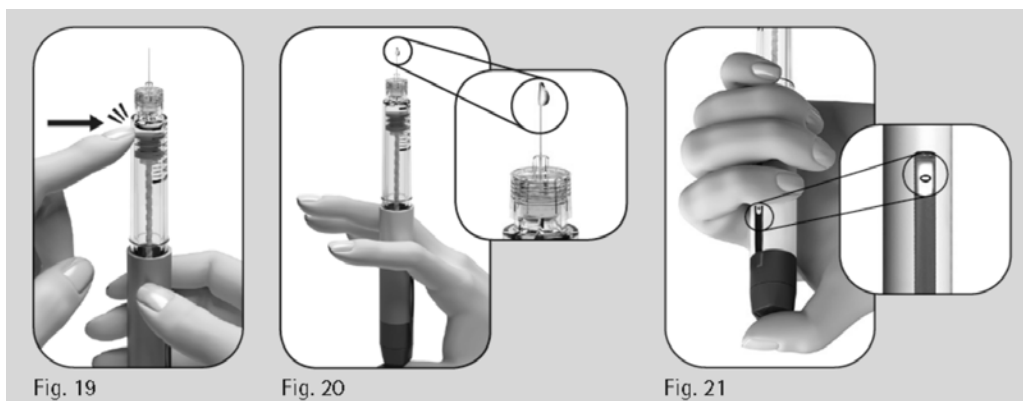


Fig. 19

Fig. 20

Fig. 21

2. Hold the pen with the needle pointing upward.
3. Tap the reservoir holder gently (Figure 19).
4. Press the dose setting knob **as far as it will go**. A tiny droplet of liquid will appear at the tip of the needle (Figure 20).
5. Check that the **Dose Feedback Window** reads “0” (Figure 21).
6. Proceed to **Step 4 Dial your dose.**

If a tiny droplet of liquid does not appear, contact your healthcare provider.

Step 4 Dial your dose

Note: The pen contains 150 IU follitropin alfa. The 150 IU pen maximum single-dose setting is 150 IU. The smallest single-dose setting is 12.5 IU and the dose can be increased in increments of 12.5 IU.

- 4.1 Turn the dose setting knob until your intended dose shows in the Dose Feedback Window.
- Example: If your intended dose is “150” IU, confirm that the Dose Feedback Window reads “150” (Figure 22). Injecting an incorrect amount of medicine could affect your treatment.

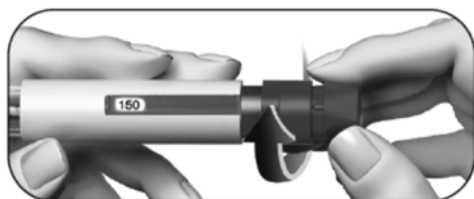


Fig. 22

- Turn the dose setting knob **forward** to dial up (Figure 22).

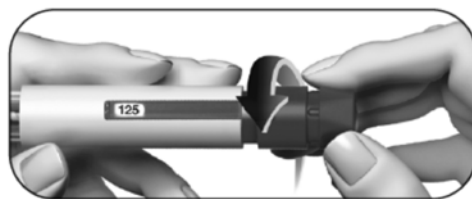


Fig. 23

- You can turn the dose setting knob **backwards** if you turn it past your intended dose (Figure 23).

- 4.2. Check that the **Dose Feedback Window** displays your **complete prescribed dose** before you move on to the next step.

Step 5 Inject your dose

Important: Inject the dose as you were trained to do by your healthcare provider.

- 5.1 Slowly push the needle into the skin entirely (Figure 24).



Fig. 24

- 5.2 Place your thumb in the middle of the dose setting knob. **Slowly press the dose knob down as far as it will go** and hold it to complete the full injection (Figure 25).

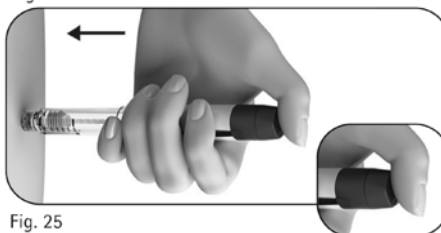


Fig. 25

Note: The larger the dose, the longer it will take to inject.

- 5.3 Hold the dose knob down for a minimum of 5 seconds before you remove the needle from your skin (Figure 26).

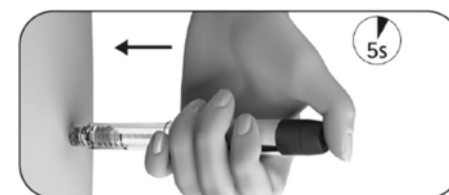


Fig. 26

- The dose number shown in the **Dose Feedback Window** will turn back to “0”.
- After a minimum of 5 seconds, pull the needle out of the skin **while keeping the dose setting knob pressed down** (Figure 27).
- When the needle is out of the skin, release the dose setting knob.

Do not release the dose knob until you remove the needle from the skin.

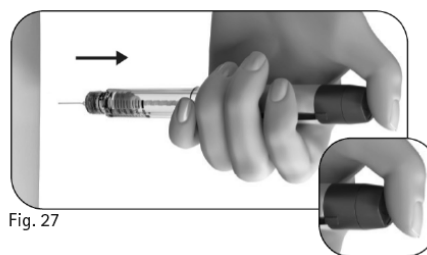


Fig. 27

Step 6 Remove the needle after each injection

- 6.1 Place the outer needle cap on a flat surface.
- 6.2 Hold the GONAL-f pre-filled pen firmly with one hand and slip the needle into the outer needle cap (Figure 28).
- 6.3 Continue by pushing the capped needle against a firm surface until you hear a “click” (Figure 29).
- 6.4 Grip the outer needle cap and unscrew the needle by turning it in the opposite direction (Figure 30).
- 6.5 Dispose of the used needle safely in a sharps container (Figure 31). Handle the needle with care to avoid getting injured by the needle.



Fig. 28



Fig. 29



Fig. 30



Fig. 31

Do not reuse or share any used needle.

Step 7 After the injection

- 7.1 Check you have given a complete injection:

- Check that the Dose Feedback Window shows “0” (Figure 32).

If the Dose Feedback Window shows “0”, you have completed your dose.

If the Dose Feedback Window shows a number **higher than “0”**, the GONAL-f pre-filled pen is empty. You have not received your full prescribed dose and you must perform step 7.2 below.



Fig. 32

- 7.2 Complete a partial injection (only when needed):

- The **Dose Feedback Window** will indicate the missing amount you need to inject using a new pen. In the example shown, the missing amount is “50” IU (Figure 33).

To complete the dose with a second pen, repeat Steps 1 through 8.



Fig. 33

Step 8 Store the GONAL-f pre-filled pen

- 8.1 Put the pen cap back onto the pen to avoid infection (Figure 34).
- 8.2 Store the pen with the cap on it in a safe place and as indicated in the Package Leaflet.
- 8.3 When the pen is empty, ask your healthcare provider how to dispose of it.

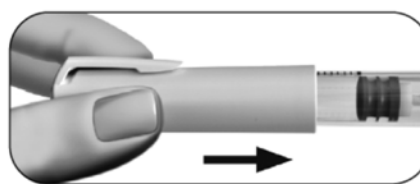


Fig. 34

Do not store the pen with the needle still attached, as this may cause infection.

Do not reuse the GONAL-f pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

Contact your healthcare provider if you have questions.

GONAL-f pre-filled pen treatment diary

1 Treatment Day Number	2 Date	3 Time	4 Pen Volume 150 IU/0.24 ml	5 Prescribed Dose	6 Amount Set to Inject	7 Dose Feedback Window		8 Amount to Be Set for a Second Injection
	/	:	150 IU			<input type="checkbox"/> if "0", injection complete		<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	150 IU			<input type="checkbox"/> if "0", injection complete		<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	150 IU			<input type="checkbox"/> if "0", injection complete		<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
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This Instructions for Use has been last revised in: {MM/YYYY}.

Package leaflet: Information for the user

GONAL-f 300 IU/0.48 mL solution for injection in pre-filled pen follitropin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What GONAL-f is and what it is used for
 2. What you need to know before you use GONAL-f
 3. How to use GONAL-f
 4. Possible side effects
 5. How to store GONAL-f
 6. Contents of the pack and other information
- Instructions for use

1. What GONAL-f is and what it is used for

What GONAL-f is

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.

What GONAL-f is used for

In adult women, GONAL-f is used:

- to help release an egg from the ovary (ovulation) in women that cannot ovulate and that did not respond to treatment with a medicine called “clomiphene citrate”.
- together with another medicine called “lutropin alfa” (“luteinising hormone” or LH) to help release egg from the ovary (ovulation) in women whose body is producing very little gonadotropins (FSH and LH).
- to help develop several follicles (each containing an egg) in women undergoing assisted reproductive technology procedures (procedures that may help you to become pregnant) such as “*in vitro* fertilisation”, “gamete intra-fallopian transfer” or “zygote intra-fallopian transfer”.

In adult men, GONAL-f is used:

- together with another medicine called “human chorionic gonadotropin” (hCG) to help produce sperm in men that are infertile due to a low level of certain hormones.

2. What you need to know before you use GONAL-f

You and your partner’s fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility disorders.

Do not use GONAL-f

- if you are allergic to follicle stimulating hormone or any of the other ingredients of this medicine listed in section 6.
- if you have a tumour in your hypothalamus or pituitary gland (both are parts of the brain).
- if you are **a woman**:
 - with large ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
 - with unexplained vaginal bleeding.
 - with cancer in your ovaries, womb or breasts.
 - with a condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), or malformed reproductive organs.
- if you are **a man**:
 - with damaged testicles that cannot be healed.

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Gonal-f.

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).

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.

Ovarian hyper-stimulation syndrome (OHSS)

If you are a woman, this medicine increases your risk of developing OHSS. This is when your follicles develop too much and become large cysts. If you get lower abdominal pain, gain any weight rapidly, feel sick or are vomiting or if you have difficulty in breathing, talk to your doctor straight away who might ask you to stop using this medicine (see section 4).

In case you are not ovulating, and if the recommended dose and schedule of administration are adhered to, the occurrence of OHSS is less likely. GONAL-f treatment seldom causes severe OHSS unless the medicine that is used for final follicular maturation (containing human chorionic gonadotropin, 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.

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. When undergoing assisted reproductive technology, the risk of having a multiple pregnancy is related to your age, the quality and the number of fertilised eggs or embryos placed inside you.

Miscarriage

When undergoing assisted reproductive technology or stimulation of your ovaries to produce eggs, you are more likely to have a miscarriage than the average woman.

Blood clotting problems (thromboembolic events)

If you had in the past or recently blood clots in the leg or in the lung, or a heart attack or stroke, or if those happened in your family, then you might have a higher risk that these problems occur or become worse with GONAL-f treatment.

Men with too much FSH in their blood

If you are a man, having too much FSH in your blood can be a sign of damaged testicles. GONAL-f usually does not work if you have this problem.

If your doctor decides to try GONAL-f treatment, to monitor the treatment, they may ask you to provide semen for analysis 4 to 6 months after starting treatment.

Children and adolescents

GONAL-f is not for use in children and adolescents below 18 years old.

Other medicines and GONAL-f

Tell your doctor if you are taking, have recently taken or might take any other medicines.

- If you use GONAL-f with other medicines which help ovulation (such as hCG or clomiphene citrate), this may increase the response of your follicles.
- If you use GONAL-f at the same time as a “gonadotropin-releasing hormone” (GnRH) agonist or antagonist (these medicines reduce your sex hormone levels and stop you ovulating) you may need a higher dose of GONAL-f to produce follicles.

Pregnancy and breast-feeding

Do not use GONAL-f if you are pregnant or breast-feeding.

Driving and using machines

It is not expected that this medicine will affect your ability to drive and use machines.

GONAL-f contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially “sodium-free”.

3. How to use GONAL-f

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Using this medicine

- GONAL-f is intended to be given by injection just under the skin (subcutaneously). 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.
- If you administer GONAL-f to yourself, please carefully read and follow the “Instructions for use”.

How much to use

Your doctor will decide how much medicine you will take and how often. The doses described below are stated in International Units (IU).

Women

If you are not ovulating and have irregular or no periods.

- GONAL-f is usually given every day.
- If you have irregular periods, start using GONAL-f within the first 7 days of your menstrual cycle. If you do not have periods you can start using the medicine on any convenient day.
- The usual starting dose of GONAL-f is 75 to 150 IU each day.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- The maximum daily dose of GONAL-f is usually not higher than 225 IU.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last GONAL-f injection. The best time to have sex is on the day of the hCG injection and the day after.

If your doctor cannot see a desired response after 4 weeks, that treatment cycle with GONAL-f should be stopped. For the following treatment cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you have been diagnosed with very low levels of FSH and LH hormones

- The usual starting dose of GONAL-f is 75 to 150 IU together with 75 IU of lutropin alfa.
- You will use these two medicines each day for up to five weeks.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last injections of GONAL-f and lutropin alfa. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on your doctor’s judgment.

If your doctor cannot see a response after 5 weeks, that treatment cycle with GONAL-f should be stopped. For the following cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment with GONAL-f will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you need to develop several eggs for collection prior to any assisted reproductive technology

- The usual starting dose of GONAL-f is 150 to 225 IU each day, from day 2 or 3 of your treatment cycle.
- GONAL-f dose may be increased, depending on your response. The maximum daily dose is 450 IU.
- Treatment is continued until your eggs have developed to a desired point. This usually takes about 10 days but can take any time between 5 and 20 days. Your doctor will use blood tests and/or an ultrasound machine to check when this is.
- When your eggs are ready, you will be given a single injection of 250 micrograms “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special recombinant DNA technique), or 5 000 IU to 10 000 IU of hCG, 24 to 48 hours after the last GONAL-f injection. This gets your eggs ready for collection.

In other cases, your doctor may first stop you from ovulating by using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Then GONAL-f is started approximately two weeks after start of agonist treatment. The GONAL-f and GnRH agonist are then both given until your follicles develop as desired. For example, after two weeks of GnRH agonist treatment, 150 to 225 IU GONAL-f is administered for 7 days. The dose is then adjusted according to your ovarian response.

Men

- The usual dose of GONAL-f is 150 IU together with hCG.
- You will use these two medicines three times a week for at least 4 months.
- If you have not responded to treatment after 4 months, your doctor may suggest that you continue using these two medicines for at least 18 months.

If you use more GONAL-f than you should

The effects of taking too much GONAL-f are unknown. Nevertheless, one could expect ovarian hyper-stimulation syndrome (OHSS) to occur, which is described in section 4. However, the OHSS will only occur if hCG is also administered (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”).

If you forget to use GONAL-f

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.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects in women

- Lower abdominal pain together with nausea or vomiting may be the symptoms of ovarian hyper-stimulation syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed (see also in section 2. under “Ovarian hyper-stimulation syndrome (OHSS)”). This side effect is common (may affect up to 1 in 10 people).
- 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 side effect is uncommon (may affect up to 1 in 100 people).
- Complications of OHSS such as twisting of ovaries or blood clotting may occur rarely (may affect up to 1 in 1 000 people).
- Serious blood clotting complications (thromboembolic events) sometimes independent of OHSS may be found very rarely (may affect up to 1 in 10 000 people). This could cause chest pain, breathlessness, stroke or heart attack (see also in section 2. under “Blood clotting problems”).

Serious side effects in men and women

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing can sometimes be serious. This side effect is very rare (may affect up to 1 in 10 000 people).

If you notice any of the above-listed side effects, you should immediately contact your doctor who might ask you to stop using GONAL-f.

Other side effects in women

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

- Abdominal pain
- Feeling sick, vomiting, diarrhoea, abdominal cramps and bloating

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Other side effects in men

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

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

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty in breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GONAL-f

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the cartridge label or carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Before opening and within its shelf life, the product may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months and must be discarded if it has not been used within these 3 months.

Keep the cap on the pen, 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.

Please write on the GONAL-f pre-filled pen the day you first use it. For this purpose, a sticker is provided with the “Instructions for use”.

- Once opened, the pen should be stored between 2°C and 25°C for a maximum of 28 days.
- 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 throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What GONAL-f contains

- The active substance is follitropin alfa.
- Each pre-filled pen with multidose cartridge contains 300 IU (22 micrograms) of follitropin alfa in 0.48 mL solution.
- The other ingredients are poloxamer 188, sucrose, methionine, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, m-cresol, as well as concentrated phosphoric acid and sodium hydroxide for pH adjustment and water for injections.

What GONAL-f looks like and contents of the pack

- GONAL-f is presented as a clear, colourless liquid for injection in a pre-filled pen.
- It is supplied in packs with 1 pre-filled pen and 8 disposable needles.

Marketing Authorisation Holder

Merck Europe B.V., Gustav Mahlerplein 102, 1082 MA Amsterdam, The Netherlands

Manufacturer

Merck Serono S.p.A., Via delle Magnolie 15, 70026 Modugno (Bari), Italy

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

Instructions for use

GONAL-f PRE-FILLED PEN 300 IU/0.48 mL

Solution for injection in pre-filled pen

Follitropin alfa

Table of Contents

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How to use your GONAL-f pre-filled pen treatment diary

Get familiar with your GONAL-f pre-filled pen

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Step 2 Get ready for injection

Step 3 Attach your needle

Step 4 Dial your dose

Step 5 Inject your dose

Step 6 Remove the needle after each injection

Step 7 After the injection

Step 8 Store the GONAL-f pre-filled pen

GONAL-f pre-filled pen treatment diary

Important information about the GONAL-f pre-filled pen

- Read the Instructions for Use and the Package Leaflet before using your GONAL-f pre-filled pen.
- Always follow all directions in this Instructions for Use and training provided by your healthcare provider as they may differ from your past experience. This information will allow to prevent incorrect treatment or infection by needle stick or broken glass injury.
- The GONAL-f pre-filled pen is for subcutaneous injection only.
- Only use the GONAL-f pre-filled pen if your healthcare provider trains you on how to use it correctly.
- Your healthcare provider will tell you how many GONAL-f pre-filled pens you need to complete your treatment.
- Give yourself the injection at the same time each day.
- The numbers in the **Dose Feedback Window** represent the number of International Units, or IUs, and show the dose of follitropin alfa. Your healthcare provider will tell you how many IUs of follitropin alfa to inject each day.
- The numbers displayed in the **Dose Feedback Window** help you to:

- a. Dial your prescribed dose (Figure 1).



Fig. 1

- b. Verify a complete injection (Figure 2).



Fig. 2

- c. Read the dose remaining to be injected with a second pen (Figure 3).

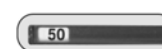


Fig. 3

- Remove the needle from the pen immediately after each injection.

Do not reuse needles.

Do not share the pen and/or needles with another person.

Do not use the GONAL-f pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.


How to use your GONAL-f pre-filled pen treatment diary

A treatment diary is included on the last page. Use the treatment diary to record the amount injected. Injecting an incorrect amount of medicine could affect your treatment.

- Record the treatment day number (column 1), date (column 2), time of your injection (column 3), and volume of your pen (column 4).
- Record your prescribed dose (column 5).
- Check you dial the right dose before injecting (column 6).
- After injection, read the number shown in the **Dose Feedback Window**.
- Confirm you receive a complete injection (column 7) or record the number shown in the **Dose Feedback Window** if other than “0” (column 8).
- When needed, inject yourself using a second pen, dialing your remaining dose written in the “Amount to Be Set for a Second Injection” section (column 8).
- Record this remaining dose in the “**Amount Set to Inject**” section (column 6) in the next row.

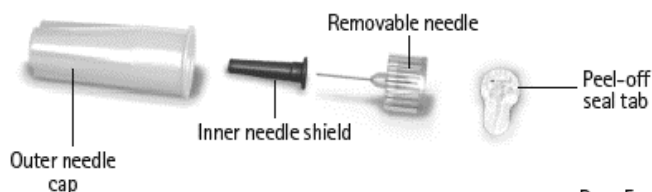
Using your treatment diary to record your daily injection(s) allows you to verify every day that you received the full prescribed dose.

An example of a treatment diary:

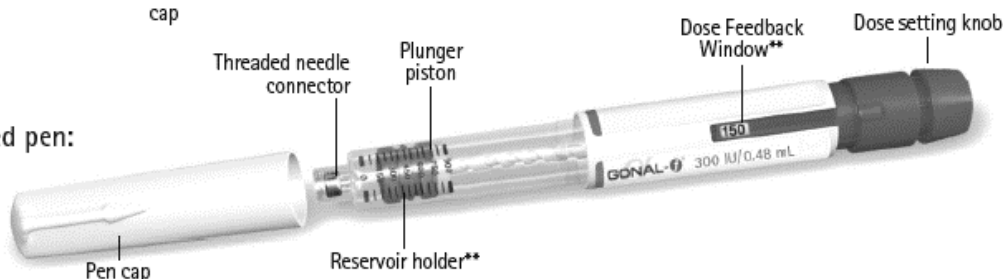
1 Treatment Day Number	2 Date	3 Time	4 Pen Volume <small>300 IU/0.48 mL</small>	5 Prescribed Dose	6 7 8		
					Dose Feedback Window		
					Amount Set to Inject	Amount to Be Set for a Second Injection	
							
#1	10/06	07:00	300 IU	125	125	<input checked="" type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
#2	11/06	07:00	300 IU	125	125	<input checked="" type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
#3	12/06/	07:00	300 IU	125	125	<input type="checkbox"/> if "0", injection complete	<input checked="" type="checkbox"/> if not "0", need second injection Inject this amount 75 using new pen
#3	12/06	07:00	300 IU	N/A	75	<input checked="" type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen

Get familiar with your GONAL-f pre-filled pen

Your needle*:



Your pre-filled pen:



*For illustrations purposes only.

The numbers in the **Dose Feedback Window and reservoir holder represent the number of International Units (IU) of medicine.

Step 1 Gather your supplies

- 1.1 Let the pre-filled pen sit at room temperature for at least 30 minutes before use to allow the medicine to reach room temperature.

Do not use a microwave or other heating element to warm up the pen.

- 1.2 Prepare a clean area and a flat surface, such as a table or countertop, in a well-lit area.

- 1.3 You will also need (not included in the pack):

- Alcohol swabs and a sharps container (Figure 4).

- 1.4 Wash your hands with soap and water and dry them well (Figure 5).

- 1.5 Use your hand to remove the GONAL-f pre-filled pen from the pack.

Do not use any tools, using tools might damage the pen.

- 1.6 Check the name on the pre-filled pen says GONAL-f.

- 1.7 Check the expiration date on the pen label (Figure 6).

Do not use the GONAL-f pre-filled pen if the expiration date has passed or if your pre-filled pen does not say GONAL-f.



Fig. 4



Fig. 5

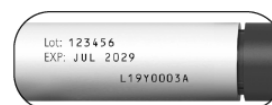


Fig. 6

Step 2 Get ready for injection

- 2.1 Pull-off the pen cap (Figure 7).

- 2.2 Check that medicine is clear, colourless and does not contain particles.

Do not use the pre-filled pen if the medicine is discolored or cloudy, as this can cause an infection.

- 2.3 Check that the Dose Feedback Window is set to "0" (Figure 8).

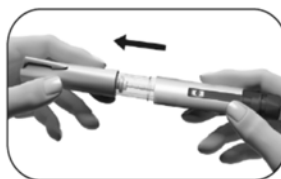


Fig. 7

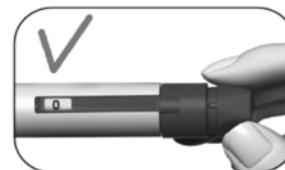


Fig. 8

Choose your injection site:

2.4 Your healthcare provider should show you the injection sites to use around your stomach area (Figure 9). To minimise skin irritation, select a different injection site each day.

2.5 Clean the skin at the injection site by wiping with an alcohol swab.

Do not touch or cover the cleaned skin.

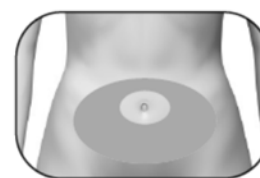


Fig. 9

Step 3 Attach your needle

Important: Always make sure to use a new needle for each injection. Re-using needles can cause infection.

3.1 Get a new needle. Only use the “single-use” needles supplied.

3.2 Check that the outer needle cap is not damaged.

3.3 Hold the outer needle cap firmly.

3.4 Check that the peel-off seal on the outer needle cap is not damaged or loose, and that expiration date has not passed (Figure 10).

3.5 Remove the peel-off seal (Figure 11).

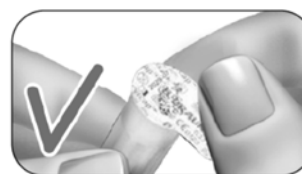


Fig. 10



Fig. 11

Do not use the needle if it is damaged, expired or if the outer needle cap or the peel-off seal is damaged or loose. Using expired needles or needles with damaged peel-off seal or outer needle cap can lead to infection. Throw it away in a sharps container and get a new needle.

3.6 Screw the outer needle cap onto the threaded tip of the GONAL-f pre-filled pen until you feel a light resistance (Figure 12).

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

3.7 Remove the outer needle cap by pulling it gently (Figure 13).

3.8 Put it aside for later use (Figure 14).

Do not discard the outer needle cap, as it will prevent needle stick injury and infection when detaching the needle from the pre-filled pen.

3.9 Hold the GONAL-f pre-filled pen with the needle pointing upward (Figure 15).

3.10 Carefully remove and discard the green inner needle shield (Figure 16).

Do not recap the needle with the green inner needle shield, as it can lead to needle stick injury and infection.

3.11 Look closely at the tip of the needle for tiny droplet(s) of liquid.

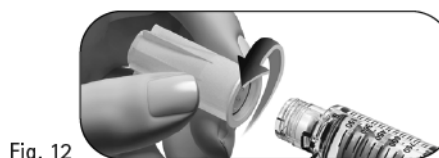


Fig. 12



Fig. 13



Fig. 14

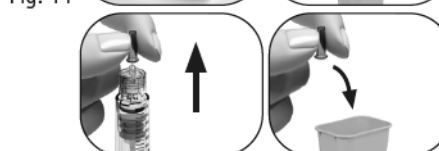


Fig. 15



Fig. 16

If	Then
Using a new pen	<p>Check for a droplet of liquid at the tip of the needle (Figure 17).</p> <ul style="list-style-type: none"> • If you see a tiny droplet of liquid, proceed to Step 4 Dial your dose. • If you do not see a tiny droplet at or near the needle tip, you must perform the steps on the next page to remove air in the system.
Reusing a pen	It is NOT required to check for a droplet of liquid. Proceed directly to Step 4 Dial your dose.

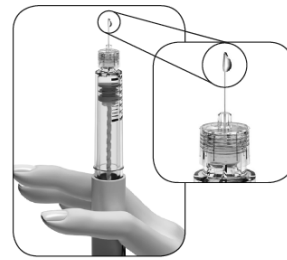


Fig. 17

If you do not see a tiny droplet(s) of liquid at or near the tip the first time you use a new pen:

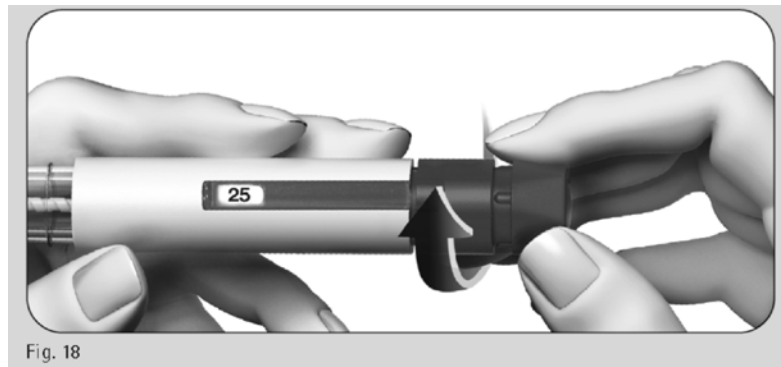
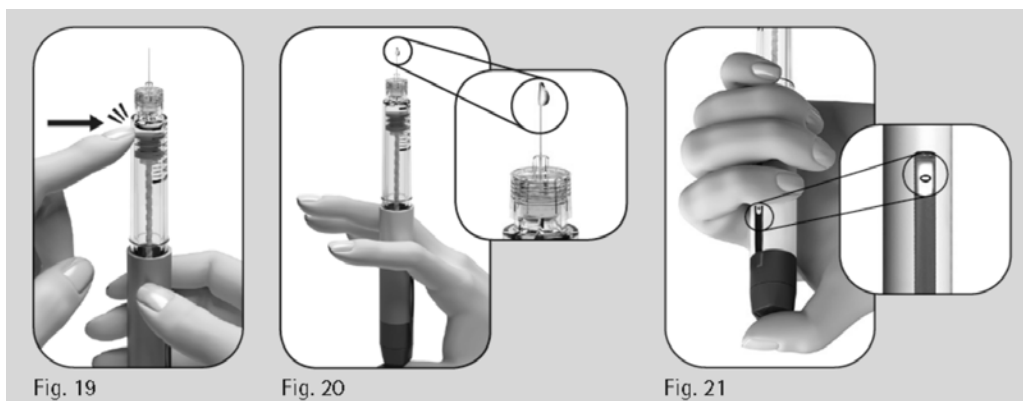


Fig. 18

1. Gently turn the dose setting knob forward until it **reads “25”** in the **Dose Feedback Window** (Figure 18).
 - You can turn the dose knob backward if you turn it past “25”.



2. Hold the pen with the needle pointing upward.
3. Tap the reservoir holder gently (Figure 19).
4. Press the dose setting knob **as far as it will go**. A tiny droplet of liquid will appear at the tip of the needle (Figure 20).
5. Check that the **Dose Feedback Window** reads “0” (Figure 21).
6. Proceed to **Step 4 Dial your dose.**

If a tiny droplet of liquid does not appear, contact your healthcare provider.

Step 4 Dial your dose

Note: The pen contains 300 IU follitropin alfa. The 300 IU pen maximum single-dose setting is 300 IU. The smallest single-dose setting is 12.5 IU and the dose can be increased in increments of 12.5 IU.

- 4.1 Turn the dose setting knob until your intended dose shows in the Dose Feedback Window.
- Example: If your intended dose is “150” IU, confirm that the Dose Feedback Window reads “150” (Figure 22). Injecting an incorrect amount of medicine could affect your treatment.

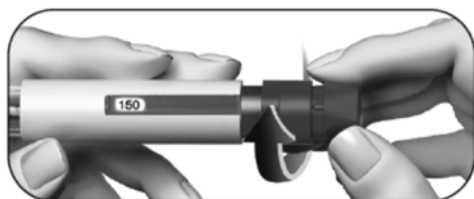


Fig. 22

- Turn the dose setting knob **forward** to dial up (Figure 22).

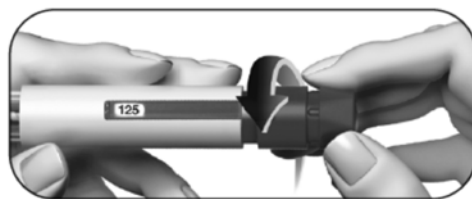


Fig. 23

- You can turn the dose setting knob **backwards** if you turn it past your intended dose (Figure 23).

- 4.2. Check that the **Dose Feedback Window** displays your **complete prescribed dose** before you move on to the next step.

Step 5 Inject your dose

Important: Inject the dose as you were trained to do by your healthcare provider.

- 5.1 Slowly push the needle into the skin entirely (Figure 24).

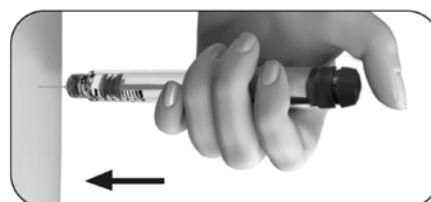


Fig. 24

- 5.2 Place your thumb in the middle of the dose setting knob. **Slowly press the dose knob down as far as it will go** and hold it to complete the full injection (Figure 25).

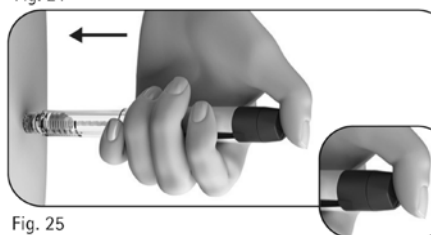


Fig. 25

Note: The larger the dose, the longer it will take to inject.

- 5.3 Hold the dose knob down for a minimum of 5 seconds before you remove the needle from your skin (Figure 26).

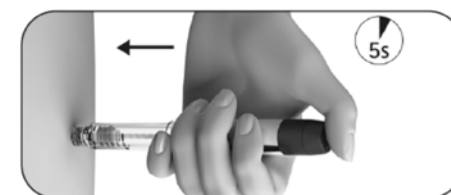


Fig. 26

- The dose number shown in the **Dose Feedback Window** will turn back to “0”.
- After a minimum of 5 seconds, pull the needle out of the skin **while keeping the dose setting knob pressed down** (Figure 27).
- When the needle is out of the skin, release the dose setting knob.

Do not release the dose knob until you remove the needle from the skin.

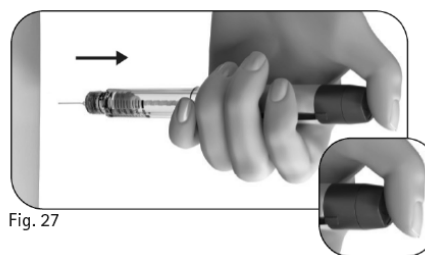


Fig. 27

Step 6 Remove the needle after each injection

- 6.1 Place the outer needle cap on a flat surface.
- 6.2 Hold the GONAL-f pre-filled pen firmly with one hand and slip the needle into the outer needle cap (Figure 28).
- 6.3 Continue by pushing the capped needle against a firm surface until you hear a “click” (Figure 29).
- 6.4 Grip the outer needle cap and unscrew the needle by turning it in the opposite direction (Figure 30).
- 6.5 Dispose of the used needle safely in a sharps container (Figure 31). Handle the needle with care to avoid getting injured by the needle.



Fig. 28



Fig. 29



Fig. 30



Fig. 31

Do not reuse or share any used needle.

Step 7 After the injection

- 7.1 Check you have given a complete injection:

- Check that the Dose Feedback Window shows “0” (Figure 32).

If the Dose Feedback Window shows “0”, you have completed your dose.

If the Dose Feedback Window shows a number **higher than “0”**, the GONAL-f pre-filled pen is empty. You have not received your full prescribed dose and you must perform step 7.2 below.



Fig. 32

- 7.2 Complete a partial injection (only when needed):

- The **Dose Feedback Window** will indicate the missing amount you need to inject using a new pen. In the example shown, the missing amount is “50” IU (Figure 33).

To complete the dose with a second pen, repeat Steps 1 through 8.



Fig. 33

Step 8 Store the GONAL-f pre-filled pen

- 8.1 Put the pen cap back onto the pen to avoid infection (Figure 34).
- 8.2 Store the pen with the cap on it in a safe place and as indicated in the Package Leaflet.
- 8.3 When the pen is empty, ask your healthcare provider how to dispose of it.

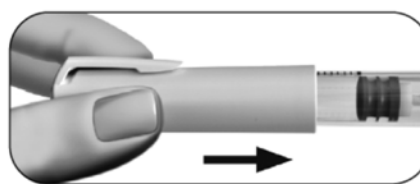


Fig. 34

Do not store the pen with the needle still attached, as this may cause infection.

Do not reuse the GONAL-f pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

Contact your healthcare provider if you have questions.

GONAL-f pre-filled pen treatment diary

1 Treatment Day Number	2 Date	3 Time	4 Pen Volume <small>300 IU/0.48 ml</small>	5 Prescribed Dose	6 Amount Set to Inject	7 Dose Feedback Window 	8 Amount to Be Set for a Second Injection
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen -
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	300 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen

This Instructions for Use has been last revised in: {MM/YYYY}.

Package leaflet: Information for the user

GONAL-f 450 IU/0.72 mL solution for injection in pre-filled pen follitropin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What GONAL-f is and what it is used for
 2. What you need to know before you use GONAL-f
 3. How to use GONAL-f
 4. Possible side effects
 5. How to store GONAL-f
 6. Contents of the pack and other information
- Instructions for use

1. What GONAL-f is and what it is used for

What GONAL-f is

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.

What GONAL-f is used for

In adult women, GONAL-f is used:

- to help release an egg from the ovary (ovulation) in women that cannot ovulate and that did not respond to treatment with a medicine called “clomiphene citrate”.
- together with another medicine called “lutropin alfa” (“luteinising hormone” or LH) to help release egg from the ovary (ovulation) in women whose body is producing very little gonadotropins (FSH and LH).
- to help develop several follicles (each containing an egg) in women undergoing assisted reproductive technology procedures (procedures that may help you to become pregnant) such as “*in vitro* fertilisation”, “gamete intra-fallopian transfer” or “zygote intra-fallopian transfer”.

In adult men, GONAL-f is used:

- together with another medicine called “human chorionic gonadotropin” (hCG) to help produce sperm in men that are infertile due to a low level of certain hormones.

2. What you need to know before you use GONAL-f

You and your partner’s fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility disorders.

Do not use GONAL-f

- if you are allergic to follicle stimulating hormone or any of the other ingredients of this medicine listed in section 6.
- if you have a tumour in your hypothalamus or pituitary gland (both are parts of the brain).
- if you are **a woman**:
 - with large ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
 - with unexplained vaginal bleeding.
 - with cancer in your ovaries, womb or breasts.
 - with a condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), or malformed reproductive organs.
- if you are **a man**:
 - with damaged testicles that cannot be healed.

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Gonal-f.

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).

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.

Ovarian hyper-stimulation syndrome (OHSS)

If you are a woman, this medicine increases your risk of developing OHSS. This is when your follicles develop too much and become large cysts. If you get lower abdominal pain, gain any weight rapidly, feel sick or are vomiting or if you have difficulty in breathing, talk to your doctor straight away who might ask you to stop using this medicine (see section 4).

In case you are not ovulating, and if the recommended dose and schedule of administration are adhered to, the occurrence of OHSS is less likely. GONAL-f treatment seldom causes severe OHSS unless the medicine that is used for final follicular maturation (containing human chorionic gonadotropin, 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.

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. When undergoing assisted reproductive technology, the risk of having a multiple pregnancy is related to your age, the quality and the number of fertilised eggs or embryos placed inside you.

Miscarriage

When undergoing assisted reproductive technology or stimulation of your ovaries to produce eggs, you are more likely to have a miscarriage than the average woman.

Blood clotting problems (thromboembolic events)

If you had in the past or recently blood clots in the leg or in the lung, or a heart attack or stroke, or if those happened in your family, then you might have a higher risk that these problems occur or become worse with GONAL-f treatment.

Men with too much FSH in their blood

If you are a man, having too much FSH in your blood can be a sign of damaged testicles. GONAL-f usually does not work if you have this problem.

If your doctor decides to try GONAL-f treatment, to monitor the treatment, they may ask you to provide semen for analysis 4 to 6 months after starting treatment.

Children and adolescents

GONAL-f is not for use in children and adolescents below 18 years old.

Other medicines and GONAL-f

Tell your doctor if you are taking, have recently taken or might take any other medicines.

- If you use GONAL-f with other medicines which help ovulation (such as hCG or clomiphene citrate), this may increase the response of your follicles.
- If you use GONAL-f at the same time as a “gonadotropin-releasing hormone” (GnRH) agonist or antagonist (these medicines reduce your sex hormone levels and stop you ovulating) you may need a higher dose of GONAL-f to produce follicles.

Pregnancy and breast-feeding

Do not use GONAL-f if you are pregnant or breast-feeding.

Driving and using machines

It is not expected that this medicine will affect your ability to drive and use machines.

GONAL-f contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially “sodium-free”.

3. How to use GONAL-f

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Using this medicine

- GONAL-f is intended to be given by injection just under the skin (subcutaneously). 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.
- If you administer GONAL-f to yourself, please carefully read and follow the “Instructions for use”.

How much to use

Your doctor will decide how much medicine you will take and how often. The doses described below are stated in International Units (IU).

Women

If you are not ovulating and have irregular or no periods.

- GONAL-f is usually given every day.
- If you have irregular periods, start using GONAL-f within the first 7 days of your menstrual cycle. If you do not have periods you can start using the medicine on any convenient day.
- The usual starting dose of GONAL-f is 75 to 150 IU each day.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- The maximum daily dose of GONAL-f is usually not higher than 225 IU.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last GONAL-f injection. The best time to have sex is on the day of the hCG injection and the day after.

If your doctor cannot see a desired response after 4 weeks, that treatment cycle with GONAL-f should be stopped. For the following treatment cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you have been diagnosed with very low levels of FSH and LH hormones

- The usual starting dose of GONAL-f is 75 to 150 IU together with 75 IU of lutropin alfa.
- You will use these two medicines each day for up to five weeks.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last injections of GONAL-f and lutropin alfa. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on your doctor’s judgment.

If your doctor cannot see a response after 5 weeks, that treatment cycle with GONAL-f should be stopped. For the following cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment with GONAL-f will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you need to develop several eggs for collection prior to any assisted reproductive technology

- The usual starting dose of GONAL-f is 150 to 225 IU each day, from day 2 or 3 of your treatment cycle.
- GONAL-f dose may be increased, depending on your response. The maximum daily dose is 450 IU.
- Treatment is continued until your eggs have developed to a desired point. This usually takes about 10 days but can take any time between 5 and 20 days. Your doctor will use blood tests and/or an ultrasound machine to check when this is.
- When your eggs are ready, you will be given a single injection of 250 micrograms “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special recombinant DNA technique), or 5 000 IU to 10 000 IU of hCG, 24 to 48 hours after the last GONAL-f injection. This gets your eggs ready for collection.

In other cases, your doctor may first stop you from ovulating by using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Then GONAL-f is started approximately two weeks after start of agonist treatment. The GONAL-f and GnRH agonist are then both given until your follicles develop as desired. For example, after two weeks of GnRH agonist treatment, 150 to 225 IU GONAL-f is administered for 7 days. The dose is then adjusted according to your ovarian response.

Men

- The usual dose of GONAL-f is 150 IU together with hCG.
- You will use these two medicines three times a week for at least 4 months.
- If you have not responded to treatment after 4 months, your doctor may suggest that you continue using these two medicines for at least 18 months.

If you use more GONAL-f than you should

The effects of taking too much GONAL-f are unknown. Nevertheless, one could expect ovarian hyper-stimulation syndrome (OHSS) to occur, which is described in section 4. However, the OHSS will only occur if hCG is also administered (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”).

If you forget to use GONAL-f

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.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects in women

- Lower abdominal pain together with nausea or vomiting may be the symptoms of ovarian hyper-stimulation syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed (see also in section 2. under “Ovarian hyper-stimulation syndrome (OHSS)”). This side effect is common (may affect up to 1 in 10 people).
- 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 side effect is uncommon (may affect up to 1 in 100 people).
- Complications of OHSS such as twisting of ovaries or blood clotting may occur rarely (may affect up to 1 in 1 000 people).
- Serious blood clotting complications (thromboembolic events) sometimes independent of OHSS may be found very rarely (may affect up to 1 in 10 000 people). This could cause chest pain, breathlessness, stroke or heart attack (see also in section 2. under “Blood clotting problems”).

Serious side effects in men and women

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing can sometimes be serious. This side effect is very rare (may affect up to 1 in 10 000 people).

If you notice any of the above-listed side effects, you should immediately contact your doctor who might ask you to stop using GONAL-f.

Other side effects in women

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

- Abdominal pain
- Feeling sick, vomiting, diarrhoea, abdominal cramps and bloating

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Other side effects in men

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

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

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty in breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GONAL-f

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the cartridge label or carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Before opening and within its shelf life, the product may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months and must be discarded if it has not been used within these 3 months.

Keep the cap on the pen, 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.

Please write on the GONAL-f pre-filled pen the day you first use it. For this purpose, a sticker is provided with the “Instructions for use”.

- Once opened, the pen should be stored between 2°C and 25°C for a maximum of 28 days.
- 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 throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What GONAL-f contains

- The active substance is follitropin alfa.
- Each pre-filled pen with multidose cartridge contains 450 IU (33 micrograms) of follitropin alfa in 0.72 mL solution.
- The other ingredients are poloxamer 188, sucrose, methionine, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, m-cresol, as well as concentrated phosphoric acid and sodium hydroxide for pH adjustment and water for injections.

What GONAL-f looks like and contents of the pack

- GONAL-f is presented as a clear, colourless liquid for injection in a pre-filled pen.
- It is supplied in packs with 1 pre-filled pen and 12 disposable needles.

Marketing Authorisation Holder

Merck Europe B.V., Gustav Mahlerplein 102, 1082 MA Amsterdam, The Netherlands

Manufacturer

Merck Serono S.p.A., Via delle Magnolie 15, 70026 Modugno (Bari), Italy

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

Instructions for use

GONAL-f PRE-FILLED PEN 450 IU/0.72 mL

Solution for injection in pre-filled pen
Follitropin alfa

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Step 4 Dial your dose

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Step 7 After the injection

Step 8 Store the GONAL-f pre-filled pen

GONAL-f pre-filled pen treatment diary

Important information about the GONAL-f pre-filled pen

- Read the Instructions for Use and the Package Leaflet before using your GONAL-f pre-filled pen.
- Always follow all directions in this Instructions for Use and training provided by your healthcare provider as they may differ from your past experience. This information will allow to prevent incorrect treatment or infection by needle stick or broken glass injury.
- The GONAL-f pre-filled pen is for subcutaneous injection only.
- Only use the GONAL-f pre-filled pen if your healthcare provider trains you on how to use it correctly.
- Your healthcare provider will tell you how many GONAL-f pre-filled pens you need to complete your treatment.
- Give yourself the injection at the same time each day.
- The numbers in the **Dose Feedback Window** represent the number of International Units, or IUs, and show the dose of follitropin alfa. Your healthcare provider will tell you how many IUs of follitropin alfa to inject each day.
- The numbers displayed in the **Dose Feedback Window** help you to:

- a. Dial your prescribed dose (Figure 1).



Fig. 1

- b. Verify a complete injection (Figure 2).



Fig. 2

- c. Read the dose remaining to be injected with a second pen (Figure 3).



Fig. 3

- Remove the needle from the pen immediately after each injection.

Do not reuse needles.

Do not share the pen and/or needles with another person.

Do not use the GONAL-f pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.


How to use your GONAL-f pre-filled pen treatment diary

A treatment diary is included on the last page. Use the treatment diary to record the amount injected. Injecting an incorrect amount of medicine could affect your treatment.

- Record the treatment day number (column 1), date (column 2), time of your injection (column 3), and volume of your pen (column 4).
- Record your prescribed dose (column 5).
- Check you dial the right dose before injecting (column 6).
- After injection, read the number shown in the **Dose Feedback Window**.
- Confirm you receive a complete injection (column 7) or record the number shown in the **Dose Feedback Window** if other than “0” (column 8).
- When needed, inject yourself using a second pen, dialing your remaining dose written in the “Amount to Be Set for a Second Injection” section (column 8).
- Record this remaining dose in the “**Amount Set to Inject**” section (column 6) in the next row.

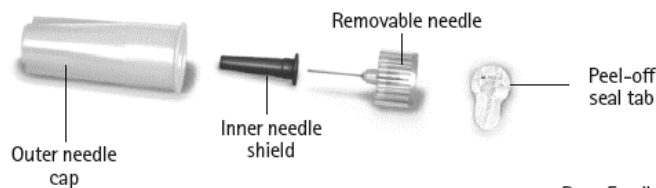
Using your treatment diary to record your daily injection(s) allows you to verify every day that you received the full prescribed dose.

An example of a treatment diary:

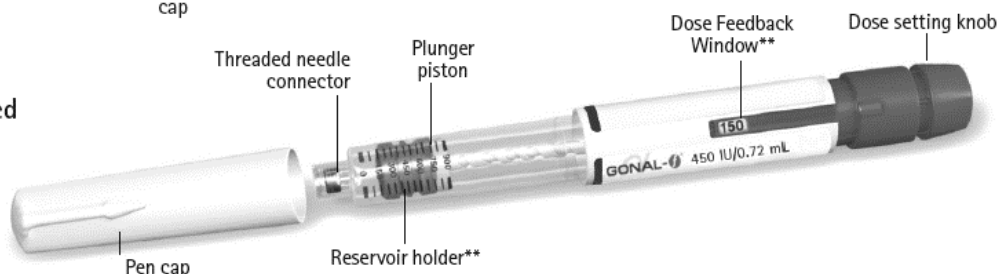
1 Treatment Day Number	2 Date	3 Time	4 Pen Volume <small>450 IU/0.72 mL</small>	5 Prescribed Dose	6 7 8		
					Dose Feedback Window		
					Amount Set to Inject	Amount to Be Set for a Second Injection	
							
#1	10/06	07:00	450 IU	175	175	<input checked="" type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
#2	11/06	07:00	450 IU	175	175	<input checked="" type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
#3	12/06/	07:00	450 IU	175	175	<input type="checkbox"/> if "0", injection complete	<input checked="" type="checkbox"/> if not "0", need second injection Inject this amount 75 using new pen
#3	12/06	07:00	450 IU	N/A	75	<input checked="" type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen

Get familiar with your GONAL-f pre-filled pen

Your needle*:



Your pre-filled pen:



*For illustrations purposes only.

**The numbers in the Dose Feedback Window and reservoir holder represent the number of International Units (IU) of medicine.

Step 1 Gather your supplies

- 1.1 Let the pre-filled pen sit at room temperature for at least 30 minutes before use to allow the medicine to reach room temperature.

Do not use a microwave or other heating element to warm up the pen.

- 1.2 Prepare a clean area and a flat surface, such as a table or countertop, in a well-lit area.

- 1.3 You will also need (not included in the pack):

- Alcohol swabs and a sharps container (Figure 4).

- 1.4 Wash your hands with soap and water and dry them well (Figure 5).

- 1.5 Use your hand to remove the GONAL-f pre-filled pen from the pack.

Do not use any tools, using tools might damage the pen.

- 1.6 Check the name on the pre-filled pen says GONAL-f.

- 1.7 Check the expiration date on the pen label (Figure 6).

Do not use the GONAL-f pre-filled pen if the expiration date has passed or if your pre-filled pen does not say GONAL-f.



Fig. 4



Fig. 5

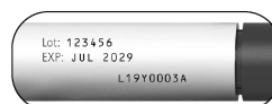


Fig. 6

Step 2 Get ready for injection

- 2.1 Pull-off the pen cap (Figure 7).

- 2.2 Check that medicine is clear, colourless and does not contain particles.

Do not use the pre-filled pen if the medicine is discolored or cloudy, as this can cause an infection.

- 2.3 Check that the Dose Feedback Window is set to "0" (Figure 8).

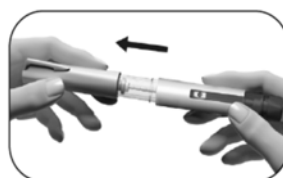


Fig. 7

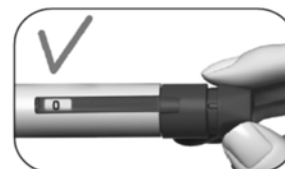


Fig. 8

Choose your injection site:

2.4 Your healthcare provider should show you the injection sites to use around your stomach area (Figure 9). To minimise skin irritation, select a different injection site each day.

2.5 Clean the skin at the injection site by wiping with an alcohol swab.

Do not touch or cover the cleaned skin.

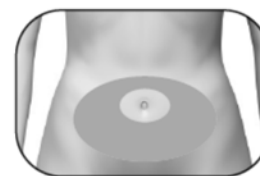


Fig. 9

Step 3 Attach your needle

Important: Always make sure to use a new needle for each injection. Re-using needles can cause infection.

3.1 Get a new needle. Only use the “single-use” needles supplied.

3.2 Check that the outer needle cap is not damaged.

3.3 Hold the outer needle cap firmly.

3.4 Check that the peel-off seal on the outer needle cap is not damaged or loose, and that expiration date has not passed (Figure 10).

3.5 Remove the peel-off seal (Figure 11).

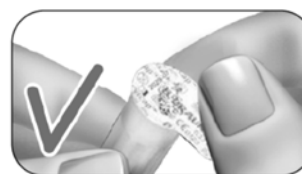


Fig. 10



Fig. 11

Do not use the needle if it is damaged, expired or if the outer needle cap or the peel-off seal is damaged or loose. Using expired needles or needles with damaged peel-off seal or outer needle cap can lead to infection. Throw it away in a sharps container and get a new needle.

3.6 Screw the outer needle cap onto the threaded tip of the GONAL-f pre-filled pen until you feel a light resistance (Figure 12).

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

3.7 Remove the outer needle cap by pulling it gently (Figure 13).

3.8 Put it aside for later use (Figure 14).

Do not discard the outer needle cap, as it will prevent needle stick injury and infection when detaching the needle from the pre-filled pen.

3.9 Hold the GONAL-f pre-filled pen with the needle pointing upward (Figure 15).

3.10 Carefully remove and discard the green inner needle shield (Figure 16).

Do not recap the needle with the green inner needle shield, as it can lead to needle stick injury and infection.

3.11 Look closely at the tip of the needle for tiny droplet(s) of liquid.

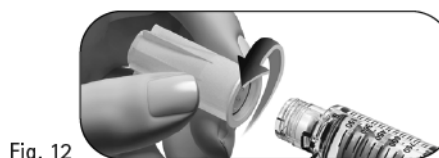


Fig. 12



Fig. 13



Fig. 14

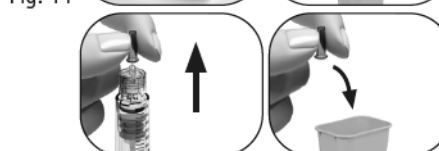


Fig. 15



Fig. 16

If	Then
Using a new pen	Check for a droplet of liquid at the tip of the needle (Figure 17). <ul style="list-style-type: none"> • If you see a tiny droplet of liquid, proceed to Step 4 Dial your dose. • If you do not see a tiny droplet at or near the needle tip, you must perform the steps on the next page to remove air in the system.
Reusing a pen	It is NOT required to check for a droplet of liquid. Proceed directly to Step 4 Dial your dose.

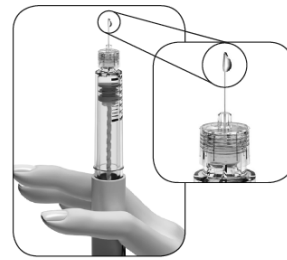


Fig. 17

If you do not see a tiny droplet(s) of liquid at or near the tip the first time you use a new pen:

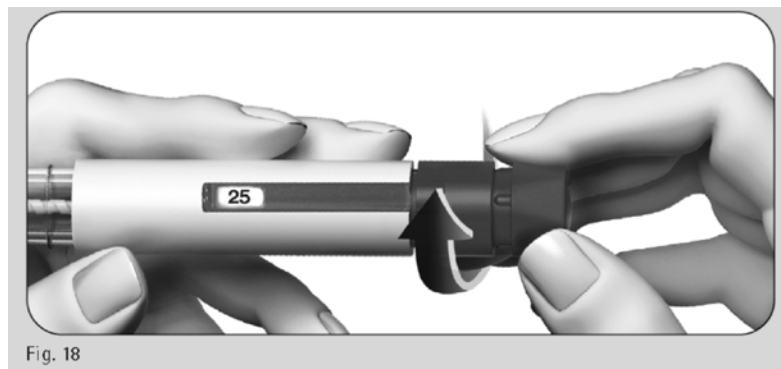


Fig. 18

1. Gently turn the dose setting knob forward until it **reads “25”** in the **Dose Feedback Window** (Figure 18).
 - You can turn the dose knob backward if you turn it past “25”.

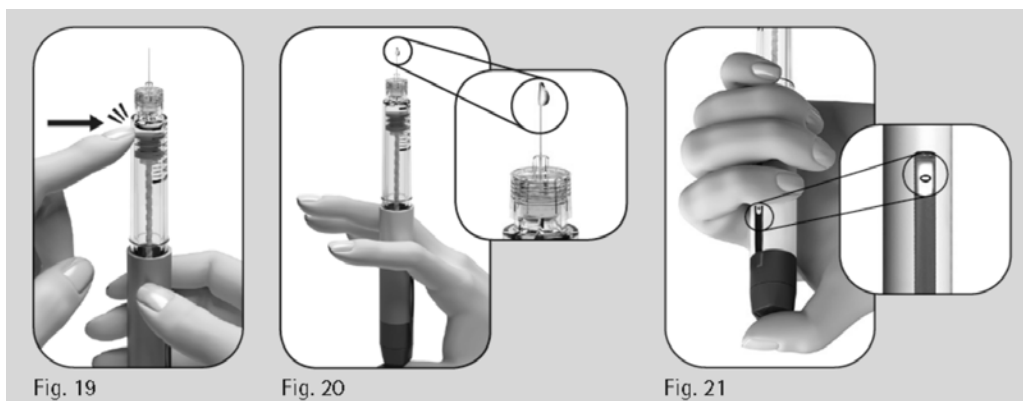


Fig. 19

Fig. 20

Fig. 21

2. Hold the pen with the needle pointing upward.
3. Tap the reservoir holder gently (Figure 19).
4. Press the dose setting knob **as far as it will go**. A tiny droplet of liquid will appear at the tip of the needle (Figure 20).
5. Check that the **Dose Feedback Window** reads “0” (Figure 21).
6. Proceed to **Step 4 Dial your dose.**

If a tiny droplet of liquid does not appear, contact your healthcare provider.

Step 4 Dial your dose

Note: The pen contains 450 IU follitropin alfa. The 450 IU pen maximum single-dose setting is 450 IU. The smallest single-dose setting is 12.5 IU and the dose can be increased in increments of 12.5 IU.

- 4.1 Turn the dose setting knob until your intended dose shows in the Dose Feedback Window.
- Example: If your intended dose is “150” IU, confirm that the Dose Feedback Window reads “150” (Figure 22). Injecting an incorrect amount of medicine could affect your treatment.

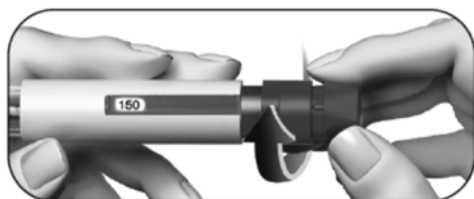


Fig. 22

- Turn the dose setting knob **forward** to dial up (Figure 22).

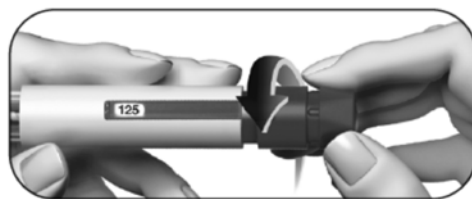


Fig. 23

- You can turn the dose setting knob **backwards** if you turn it past your intended dose (Figure 23).

- 4.2. Check that the **Dose Feedback Window** displays your **complete prescribed dose** before you move on to the next step.

Step 5 Inject your dose

Important: Inject the dose as you were trained to do by your healthcare provider.

- 5.1 Slowly push the needle into the skin entirely (Figure 24).



Fig. 24

- 5.2 Place your thumb in the middle of the dose setting knob. **Slowly press the dose knob down as far as it will go** and hold it to complete the full injection (Figure 25).

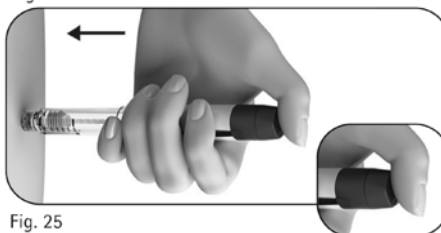


Fig. 25

Note: The larger the dose, the longer it will take to inject.

- 5.3 Hold the dose knob down for a minimum of 5 seconds before you remove the needle from your skin (Figure 26).

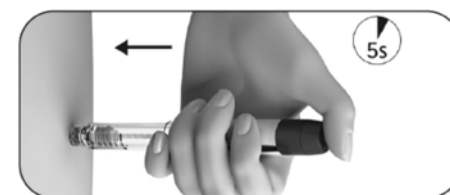


Fig. 26

- The dose number shown in the **Dose Feedback Window** will turn back to “0”.
- After a minimum of 5 seconds, pull the needle out of the skin **while keeping the dose setting knob pressed down** (Figure 27).
- When the needle is out of the skin, release the dose setting knob.

Do not release the dose knob until you remove the needle from the skin.

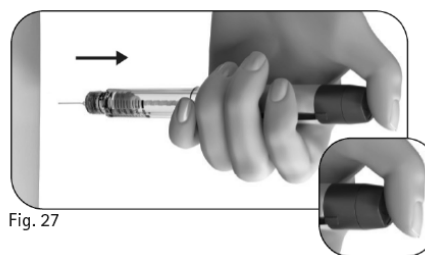


Fig. 27

Step 6 Remove the needle after each injection

- 6.1 Place the outer needle cap on a flat surface.
- 6.2 Hold the GONAL-f pre-filled pen firmly with one hand and slip the needle into the outer needle cap (Figure 28).
- 6.3 Continue by pushing the capped needle against a firm surface until you hear a “click” (Figure 29).
- 6.4 Grip the outer needle cap and unscrew the needle by turning it in the opposite direction (Figure 30).
- 6.5 Dispose of the used needle safely in a sharps container (Figure 31). Handle the needle with care to avoid getting injured by the needle.



Fig. 28



Fig. 29

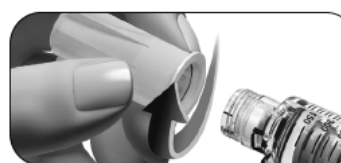


Fig. 30



Fig. 31

Do not reuse or share any used needle.

Step 7 After the injection

- 7.1 Check you have given a complete injection:

- Check that the Dose Feedback Window shows “0” (Figure 32).

If the Dose Feedback Window shows “0”, you have completed your dose.

If the Dose Feedback Window shows a number **higher than “0”**, the GONAL-f pre-filled pen is empty. You have not received your full prescribed dose and you must perform step 7.2 below.



Fig. 32

- 7.2 Complete a partial injection (only when needed):

- The **Dose Feedback Window** will indicate the missing amount you need to inject using a new pen. In the example shown, the missing amount is “50” IU (Figure 33).

To complete the dose with a second pen, repeat Steps 1 through 8.



Fig. 33

Step 8 Store the GONAL-f pre-filled pen

- 8.1 Put the pen cap back onto the pen to avoid infection (Figure 34).
- 8.2 Store the pen with the cap on it in a safe place and as indicated in the Package Leaflet.
- 8.3 When the pen is empty, ask your healthcare provider how to dispose of it.

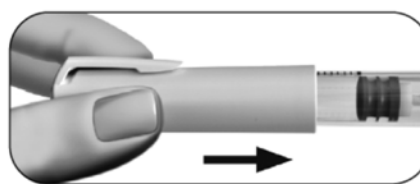



Fig. 34

Do not store the pen with the needle still attached, as this may cause infection.

Do not reuse the GONAL-f pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

Contact your healthcare provider if you have questions.

GONAL-f pre-filled pen treatment diary

1 Treatment Day Number	2 Date	3 Time	4 Pen Volume <small>450 IU/0.72 ml</small>	5 Prescribed Dose	6 Amount Set to Inject	7 Dose Feedback Window 	8 Amount to Be Set for a Second Injection
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen -
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	450 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen

This Instructions for Use has been last revised in: {MM/YYYY}.

Package leaflet: Information for the user

GONAL-f 900 IU/1.44 mL (solution for injection in pre-filled pen follitropin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What GONAL-f is and what it is used for
2. What you need to know before you use GONAL-f
3. How to use GONAL-f
4. Possible side effects
5. How to store GONAL-f
6. Contents of the pack and other information
Instructions for use

1. What GONAL-f is and what it is used for

What GONAL-f is

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.

What GONAL-f is used for

In adult women, GONAL-f is used:

- to help release an egg from the ovary (ovulation) in women that cannot ovulate and that did not respond to treatment with a medicine called “clomiphene citrate”.
- together with another medicine called “lutropin alfa” (“luteinising hormone” or LH) to help release egg from the ovary (ovulation) in women whose body is producing very little gonadotropins (FSH and LH).
- to help develop several follicles (each containing an egg) in women undergoing assisted reproductive technology procedures (procedures that may help you to become pregnant) such as “*in vitro* fertilisation”, “gamete intra-fallopian transfer” or “zygote intra-fallopian transfer”.

In adult men, GONAL-f is used:

- together with another medicine called “human chorionic gonadotropin” (hCG) to help produce sperm in men that are infertile due to a low level of certain hormones.

2. What you need to know before you use GONAL-f

You and your partner’s fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility disorders.

Do not use GONAL-f

- if you are allergic to follicle stimulating hormone or any of the other ingredients of this medicine listed in section 6.
- if you have a tumour in your hypothalamus or pituitary gland (both are parts of the brain).
- if you are **a woman**:
 - with large ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
 - with unexplained vaginal bleeding.
 - with cancer in your ovaries, womb or breasts.
 - with a condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), or malformed reproductive organs.
- if you are **a man**:
 - with damaged testicles that cannot be healed.

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Gonal-f.

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).

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.

Ovarian hyper-stimulation syndrome (OHSS)

If you are a woman, this medicine increases your risk of developing OHSS. This is when your follicles develop too much and become large cysts. If you get lower abdominal pain, gain any weight rapidly, feel sick or are vomiting or if you have difficulty in breathing, talk to your doctor straight away who might ask you to stop using this medicine (see section 4).

In case you are not ovulating, and if the recommended dose and schedule of administration are adhered to, the occurrence of OHSS is less likely. GONAL-f treatment seldom causes severe OHSS unless the medicine that is used for final follicular maturation (containing human chorionic gonadotropin, 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.

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. When undergoing assisted reproductive technology, the risk of having a multiple pregnancy is related to your age, the quality and the number of fertilised eggs or embryos placed inside you.

Miscarriage

When undergoing assisted reproductive technology or stimulation of your ovaries to produce eggs, you are more likely to have a miscarriage than the average woman.

Blood clotting problems (thromboembolic events)

If you had in the past or recently blood clots in the leg or in the lung, or a heart attack or stroke, or if those happened in your family, then you might have a higher risk that these problems occur or become worse with GONAL-f treatment.

Men with too much FSH in their blood

If you are a man, having too much FSH in your blood can be a sign of damaged testicles. GONAL-f usually does not work if you have this problem.

If your doctor decides to try GONAL-f treatment, to monitor the treatment, they may ask you to provide semen for analysis 4 to 6 months after starting treatment.

Children and adolescents

GONAL-f is not for use in children and adolescents below 18 years old.

Other medicines and GONAL-f

Tell your doctor if you are taking, have recently taken or might take any other medicines.

- If you use GONAL-f with other medicines which help ovulation (such as hCG or clomiphene citrate), this may increase the response of your follicles.
- If you use GONAL-f at the same time as a “gonadotropin-releasing hormone” (GnRH) agonist or antagonist (these medicines reduce your sex hormone levels and stop you ovulating) you may need a higher dose of GONAL-f to produce follicles.

Pregnancy and breast-feeding

Do not use GONAL-f if you are pregnant or breast-feeding.

Driving and using machines

It is not expected that this medicine will affect your ability to drive and use machines.

GONAL-f contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially “sodium-free”.

3. How to use GONAL-f

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Using this medicine

- GONAL-f is intended to be given by injection just under the skin (subcutaneously). 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.
- If you administer GONAL-f to yourself, please carefully read and follow the “Instructions for use”.

How much to use

Your doctor will decide how much medicine you will take and how often. The doses described below are stated in International Units (IU).

Women

If you are not ovulating and have irregular or no periods.

- GONAL-f is usually given every day.
- If you have irregular periods, start using GONAL-f within the first 7 days of your menstrual cycle. If you do not have periods you can start using the medicine on any convenient day.
- The usual starting dose of GONAL-f is 75 to 150 IU each day.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- The maximum daily dose of GONAL-f is usually not higher than 225 IU.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last GONAL-f injection. The best time to have sex is on the day of the hCG injection and the day after.

If your doctor cannot see a desired response after 4 weeks, that treatment cycle with GONAL-f should be stopped. For the following treatment cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you have been diagnosed with very low levels of FSH and LH hormones

- The usual starting dose of GONAL-f is 75 to 150 IU together with 75 IU of lutropin alfa.
- You will use these two medicines each day for up to five weeks.
- Your dose of GONAL-f may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- When you get the desired response, you will be given a single injection of 250 micrograms of “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last injections of GONAL-f and lutropin alfa. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on your doctor’s judgment.

If your doctor cannot see a response after 5 weeks, that treatment cycle with GONAL-f should be stopped. For the following cycle, your doctor will give you a higher starting dose of GONAL-f than before.

If your body responds too strongly, your treatment with GONAL-f will be stopped and you will not be given any hCG (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you need to develop several eggs for collection prior to any assisted reproductive technology

- The usual starting dose of GONAL-f is 150 to 225 IU each day, from day 2 or 3 of your treatment cycle.
- GONAL-f dose may be increased, depending on your response. The maximum daily dose is 450 IU.
- Treatment is continued until your eggs have developed to a desired point. This usually takes about 10 days but can take any time between 5 and 20 days. Your doctor will use blood tests and/or an ultrasound machine to check when this is.
- When your eggs are ready, you will be given a single injection of 250 micrograms “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special recombinant DNA technique), or 5 000 IU to 10 000 IU of hCG, 24 to 48 hours after the last GONAL-f injection. This gets your eggs ready for collection.

In other cases, your doctor may first stop you from ovulating by using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Then GONAL-f is started approximately two weeks after start of agonist treatment. The GONAL-f and GnRH agonist are then both given until your follicles develop as desired. For example, after two weeks of GnRH agonist treatment, 150 to 225 IU GONAL-f is administered for 7 days. The dose is then adjusted according to your ovarian response.

Men

- The usual dose of GONAL-f is 150 IU together with hCG.
- You will use these two medicines three times a week for at least 4 months.
- If you have not responded to treatment after 4 months, your doctor may suggest that you continue using these two medicines for at least 18 months.

If you use more GONAL-f than you should

The effects of taking too much GONAL-f are unknown. Nevertheless, one could expect ovarian hyper-stimulation syndrome (OHSS) to occur, which is described in section 4. However, the OHSS will only occur if hCG is also administered (see section 2, “Ovarian hyper-stimulation syndrome (OHSS)”).

If you forget to use GONAL-f

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.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects in women

- Lower abdominal pain together with nausea or vomiting may be the symptoms of ovarian hyper-stimulation syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed (see also in section 2. under “Ovarian hyper-stimulation syndrome (OHSS)”). This side effect is common (may affect up to 1 in 10 people).
- 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 side effect is uncommon (may affect up to 1 in 100 people).
- Complications of OHSS such as twisting of ovaries or blood clotting may occur rarely (may affect up to 1 in 1 000 people).
- Serious blood clotting complications (thromboembolic events) sometimes independent of OHSS may be found very rarely (may affect up to 1 in 10 000 people). This could cause chest pain, breathlessness, stroke or heart attack (see also in section 2. under “Blood clotting problems”).

Serious side effects in men and women

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing can sometimes be serious. This side effect is very rare (may affect up to 1 in 10 000 people).

If you notice any of the above-listed side effects, you should immediately contact your doctor who might ask you to stop using GONAL-f.

Other side effects in women

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

- Abdominal pain
- Feeling sick, vomiting, diarrhoea, abdominal cramps and bloating

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Other side effects in men

Very common (may affect more than 1 in 10 people):

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

Common (may affect up to 1 in 10 people):

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

Very rare (may affect up to 1 in 10 000 people):

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty in breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GONAL-f

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the cartridge label or carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Before opening and within its shelf life, the product may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to 3 months and must be discarded if it has not been used within these 3 months.

Keep the cap on the pen, 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.

Please write on the GONAL-f pre-filled pen the day you first use it. For this purpose, a sticker is provided with the “Instructions for use”.

- Once opened, the pen should be stored between 2°C and 25°C for a maximum of 28 days.
- 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 throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What GONAL-f contains

- The active substance is follitropin alfa.
- Each pre-filled pen with multidose cartridge contains 900 IU (66 micrograms) of follitropin alfa in 1.44 mL solution.
- The other ingredients are poloxamer 188, sucrose, methionine, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, m-cresol, as well as concentrated phosphoric acid and sodium hydroxide for pH adjustment and water for injections.

What GONAL-f looks like and contents of the pack

- GONAL-f is presented as a clear, colourless liquid for injection in a pre-filled pen.
- It is supplied in packs with 1 pre-filled pen and 20 disposable needles.

Marketing Authorisation Holder

Merck Europe B.V., Gustav Mahlerplein 102, 1082 MA Amsterdam, The Netherlands

Manufacturer

Merck Serono S.p.A., Via delle Magnolie 15, 70026 Modugno (Bari), Italy

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

Instructions for use

GONAL-f PRE-FILLED PEN 900 IU/1.44 mL

Solution for injection in pre-filled pen
Follitropin alfa

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Get familiar with your GONAL-f pre-filled pen

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Step 3 Attach your needle

Step 4 Dial your dose

Step 5 Inject your dose

Step 6 Remove the needle after each injection

Step 7 After the injection

Step 8 Store the GONAL-f pre-filled pen

GONAL-f pre-filled pen treatment diary

Important information about the GONAL-f pre-filled pen

- Read the Instructions for Use and the Package Leaflet before using your GONAL-f pre-filled pen.
- Always follow all directions in this Instructions for Use and training provided by your healthcare provider as they may differ from your past experience. This information will allow to prevent incorrect treatment or infection by needle stick or broken glass injury.
- The GONAL-f pre-filled pen is for subcutaneous injection only.
- Only use the GONAL-f pre-filled pen if your healthcare provider trains you on how to use it correctly.
- Your healthcare provider will tell you how many GONAL-f pre-filled pens you need to complete your treatment.
- Give yourself the injection at the same time each day.
- The numbers in the **Dose Feedback Window** represent the number of International Units, or IUs, and show the dose of follitropin alfa. Your healthcare provider will tell you how many IUs of follitropin alfa to inject each day.
- The numbers displayed in the **Dose Feedback Window** help you to:

- a. Dial your prescribed dose (Figure 1).



Fig. 1

- b. Verify a complete injection (Figure 2).



Fig. 2

- c. Read the dose remaining to be injected with a second pen (Figure 3).



Fig. 3

- Remove the needle from the pen immediately after each injection.

Do not reuse needles.

Do not share the pen and/or needles with another person.

Do not use the GONAL-f pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.


How to use your GONAL-f pre-filled pen treatment diary

A treatment diary is included on the last page. Use the treatment diary to record the amount injected. Injecting an incorrect amount of medicine could affect your treatment.

- Record the treatment day number (column 1), date (column 2), time of your injection (column 3), and volume of your pen (column 4).
- Record your prescribed dose (column 5).
- Check you dial the right dose before injecting (column 6).
- After injection, read the number shown in the **Dose Feedback Window**.
- Confirm you receive a complete injection (column 7) or record the number shown in the **Dose Feedback Window** if other than “0” (column 8).
- When needed, inject yourself using a second pen, dialing your remaining dose written in the “Amount to Be Set for a Second Injection” section (column 8).
- Record this remaining dose in the “**Amount Set to Inject**” section (column 6) in the next row.

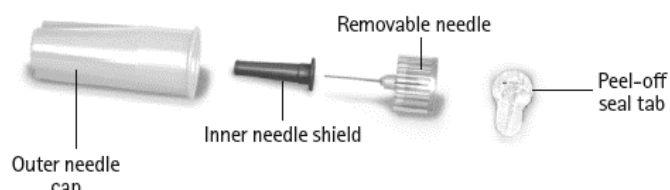
Using your treatment diary to record your daily injection(s) allows you to verify every day that you received the full prescribed dose.

An example of a treatment diary:

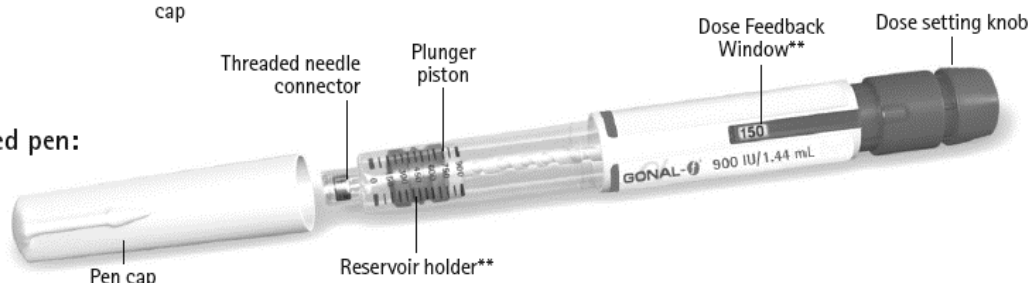
1 Treatment Day Number	2 Date	3 Time	4 Pen Volume <small>900 IU/1.44 mL</small>	5 Prescribed Dose	6 7 8		
					Dose Feedback Window		
					Amount Set to Inject		Amount to Be Set for a Second Injection
#1	10/06	07:00	900 IU	350	350	<input checked="" type="checkbox"/> if “0”, injection complete	<input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen
#2	11/06	07:00	900 IU	350	350	<input checked="" type="checkbox"/> if “0”, injection complete	<input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen
#3	12/06/	07:00	900 IU	350	350	<input type="checkbox"/> if “0”, injection complete	<input checked="" type="checkbox"/> if not “0”, need second injection Inject this amount 150 using new pen
#3	12/06	07:00	900 IU	N/A	150	<input checked="" type="checkbox"/> if “0”, injection complete	<input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen

Get familiar with your GONAL-f pre-filled pen

Your needle*:



Your pre-filled pen:



*For illustrations purposes only.

**The numbers in the Dose Feedback Window and reservoir holder represent the number of International Units (IU) of medicine.

Step 1 Gather your supplies

- 1.1 Let the pre-filled pen sit at room temperature for at least 30 minutes before use to allow the medicine to reach room temperature.

Do not use a microwave or other heating element to warm up the pen.

- 1.2 Prepare a clean area and a flat surface, such as a table or countertop, in a well-lit area.

- 1.3 You will also need (not included in the pack):

- Alcohol swabs and a sharps container (Figure 4).

- 1.4 Wash your hands with soap and water and dry them well (Figure 5).

- 1.5 Use your hand to remove the GONAL-f pre-filled pen from the pack.

Do not use any tools, using tools might damage the pen.

- 1.6 Check the name on the pre-filled pen says GONAL-f.

- 1.7 Check the expiration date on the pen label (Figure 6).

Do not use the GONAL-f pre-filled pen if the expiration date has passed or if your pre-filled pen does not say GONAL-f.



Fig. 4



Fig. 5



Fig. 6

Step 2 Get ready for injection

- 2.1 Pull-off the pen cap (Figure 7).

- 2.2 Check that medicine is clear, colourless and does not contain particles.

Do not use the pre-filled pen if the medicine is discolored or cloudy, as this can cause an infection.

- 2.3 Check that the Dose Feedback Window is set to "0" (Figure 8).

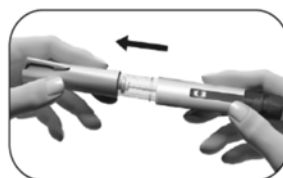


Fig. 7

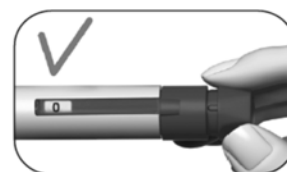


Fig. 8

Choose your injection site:

2.4 Your healthcare provider should show you the injection sites to use around your stomach area (Figure 9). To minimise skin irritation, select a different injection site each day.

2.5 Clean the skin at the injection site by wiping with an alcohol swab.

Do not touch or cover the cleaned skin.

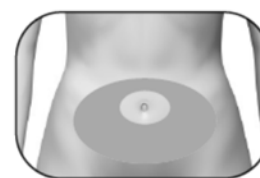


Fig. 9

Step 3 Attach your needle

Important: Always make sure to use a new needle for each injection. Re-using needles can cause infection.

3.1 Get a new needle. Only use the “single-use” needles supplied.

3.2 Check that the outer needle cap is not damaged.

3.3 Hold the outer needle cap firmly.

3.4 Check that the peel-off seal on the outer needle cap is not damaged or loose, and that expiration date has not passed (Figure 10).

3.5 Remove the peel-off seal (Figure 11).



Fig. 10



Fig. 11

Do not use the needle if it is damaged, expired or if the outer needle cap or the peel-off seal is damaged or loose. Using expired needles or needles with damaged peel-off seal or outer needle cap can lead to infection. Throw it away in a sharps container and get a new needle.

3.6 Screw the outer needle cap onto the threaded tip of the GONAL-f pre-filled pen until you feel a light resistance (Figure 12).

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

3.7 Remove the outer needle cap by pulling it gently (Figure 13).

3.8 Put it aside for later use (Figure 14).

Do not discard the outer needle cap, as it will prevent needle stick injury and infection when detaching the needle from the pre-filled pen.

3.9 Hold the GONAL-f pre-filled pen with the needle pointing upward (Figure 15).

3.10 Carefully remove and discard the green inner needle shield (Figure 16).

Do not recap the needle with the green inner needle shield, as it can lead to needle stick injury and infection.

3.11 Look closely at the tip of the needle for tiny droplet(s) of liquid.

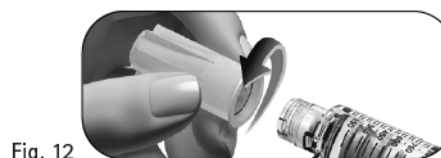


Fig. 12



Fig. 13



Fig. 14

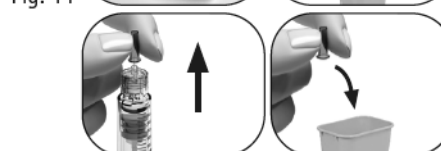


Fig. 15



Fig. 16

If	Then
Using a new pen	Check for a droplet of liquid at the tip of the needle (Figure 17). <ul style="list-style-type: none"> • If you see a tiny droplet of liquid, proceed to Step 4 Dial your dose. • If you do not see a tiny droplet at or near the needle tip, you must perform the steps on the next page to remove air in the system.
Reusing a pen	It is NOT required to check for a droplet of liquid. Proceed directly to Step 4 Dial your dose.

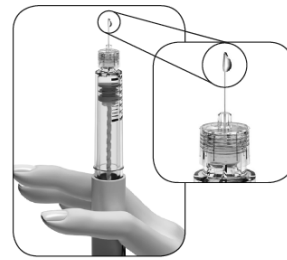


Fig. 17

If you do not see a tiny droplet(s) of liquid at or near the tip the first time you use a new pen:

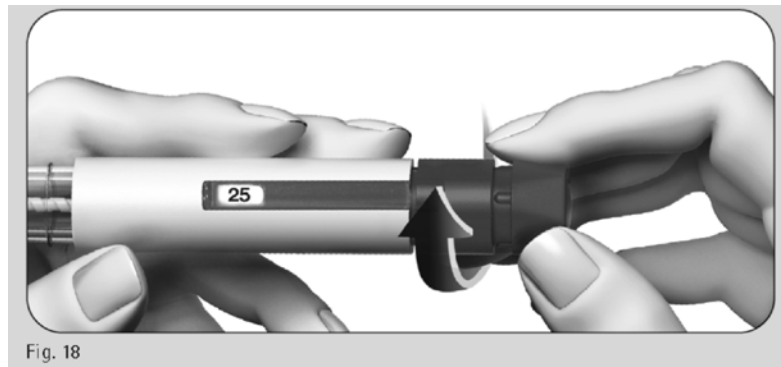


Fig. 18

1. Gently turn the dose setting knob forward until it **reads “25”** in the **Dose Feedback Window** (Figure 18).
 - You can turn the dose knob backward if you turn it past “25”.

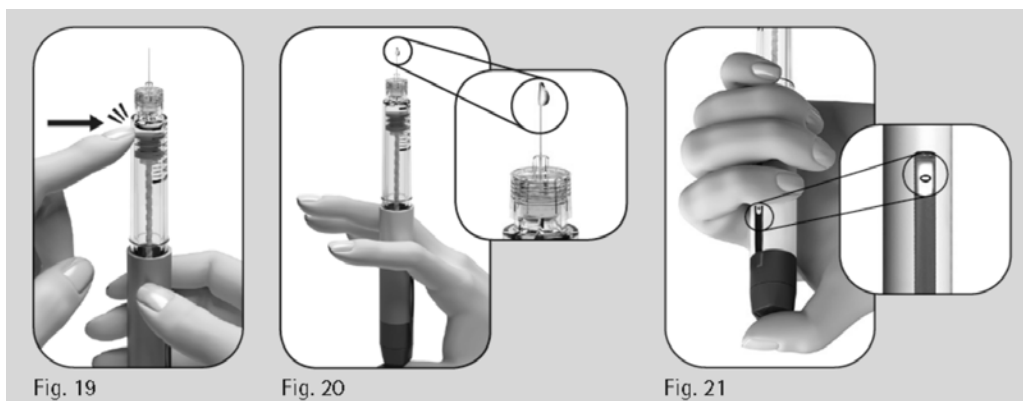


Fig. 19

Fig. 20

Fig. 21

2. Hold the pen with the needle pointing upward.
3. Tap the reservoir holder gently (Figure 19).
4. Press the dose setting knob **as far as it will go**. A tiny droplet of liquid will appear at the tip of the needle (Figure 20).
5. Check that the **Dose Feedback Window** reads “0” (Figure 21).
6. Proceed to **Step 4 Dial your dose.**

If a tiny droplet of liquid does not appear, contact your healthcare provider.

Step 4 Dial your dose

Note: The pen contains 900 IU follitropin alfa. The 900 IU pen maximum single-dose setting is 450 IU. The smallest single-dose setting is 12.5 IU and the dose can be increased in increments of 12.5 IU.

- 4.1 Turn the dose setting knob until your intended dose shows in the Dose Feedback Window.
- Example: If your intended dose is “150” IU, confirm that the Dose Feedback Window reads “150” (Figure 22). Injecting an incorrect amount of medicine could affect your treatment.

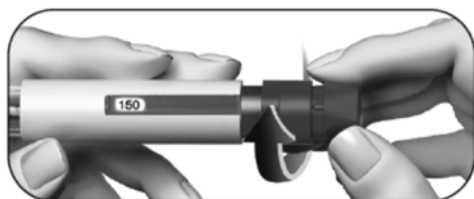


Fig. 22

- Turn the dose setting knob **forward** to dial up (Figure 22).

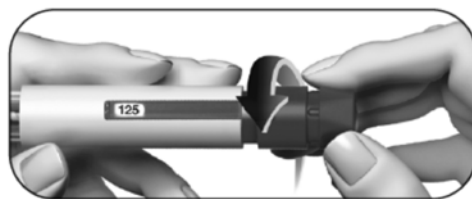


Fig. 23

- You can turn the dose setting knob **backwards** if you turn it past your intended dose (Figure 23).

- 4.2. Check that the **Dose Feedback Window** displays your **complete prescribed dose** before you move on to the next step.

Step 5 Inject your dose

Important: Inject the dose as you were trained to do by your healthcare provider.

- 5.1 Slowly push the needle into the skin entirely (Figure 24).



Fig. 24

- 5.2 Place your thumb in the middle of the dose setting knob. **Slowly press the dose knob down as far as it will go** and hold it to complete the full injection (Figure 25).

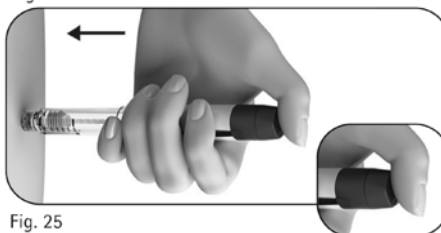


Fig. 25

Note: The larger the dose, the longer it will take to inject.

- 5.3 Hold the dose knob down for a minimum of 5 seconds before you remove the needle from your skin (Figure 26).

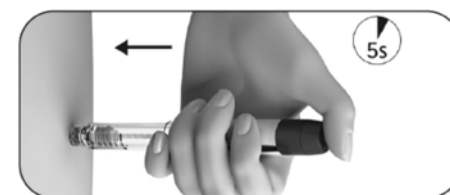


Fig. 26

- The dose number shown in the **Dose Feedback Window** will turn back to “0”.
- After a minimum of 5 seconds, pull the needle out of the skin **while keeping the dose setting knob pressed down** (Figure 27).
- When the needle is out of the skin, release the dose setting knob.

Do not release the dose knob until you remove the needle from the skin.

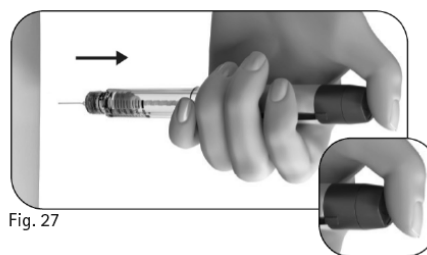


Fig. 27

Step 6 Remove the needle after each injection

- 6.1 Place the outer needle cap on a flat surface.
- 6.2 Hold the GONAL-f pre-filled pen firmly with one hand and slip the needle into the outer needle cap (Figure 28).
- 6.3 Continue by pushing the capped needle against a firm surface until you hear a “click” (Figure 29).
- 6.4 Grip the outer needle cap and unscrew the needle by turning it in the opposite direction (Figure 30).
- 6.5 Dispose of the used needle safely in a sharps container (Figure 31). Handle the needle with care to avoid getting injured by the needle.



Fig. 28



Fig. 29



Fig. 30



Fig. 31

Do not reuse or share any used needle.

Step 7 After the injection

- 7.1 Check you have given a complete injection:

- Check that the Dose Feedback Window shows “0” (Figure 32).

If the Dose Feedback Window shows “0”, you have completed your dose.

If the Dose Feedback Window shows a number **higher than “0”**, the GONAL-f pre-filled pen is empty. You have not received your full prescribed dose and you must perform step 7.2 below.



Fig. 32

- 7.2 Complete a partial injection (only when needed):

- The **Dose Feedback Window** will indicate the missing amount you need to inject using a new pen. In the example shown, the missing amount is “50” IU (Figure 33).

To complete the dose with a second pen, repeat Steps 1 through 8.



Fig. 33

Step 8 Store the GONAL-f pre-filled pen

- 8.1 Put the pen cap back onto the pen to avoid infection (Figure 34).
- 8.2 Store the pen with the cap on it in a safe place and as indicated in the Package Leaflet.
- 8.3 When the pen is empty, ask your healthcare provider how to dispose of it.

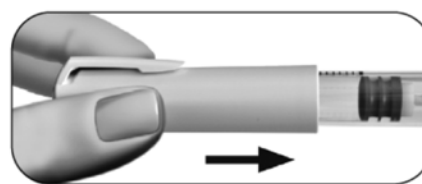



Fig. 34

Do not store the pen with the needle still attached, as this may cause infection.

Do not reuse the GONAL-f pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

Contact your healthcare provider if you have questions.

GONAL-f pre-filled pen treatment diary

1 Treatment Day Number	2 Date	3 Time	4 Pen Volume <small>900 IU/1.44 ml</small>	5 Prescribed Dose	6 Amount Set to Inject	7 Dose Feedback Window 	8 Amount to Be Set for a Second Injection
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen -
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen
	/	:	900 IU			<input type="checkbox"/> if "0", injection complete	<input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen

This Instructions for Use has been last revised in: {MM/YYYY}.