Info-Table - Version 03

MERCK

IDENTIFICATION OF THE COMPONENT	
Material component code:	N19B3403A
Local brand:	GONAL-F
Strength(s):	900 iu
TECHNICAL DATA	
Packaging site:	Merck Aubonne
Technical layout ref:	PIL_139x65_V03
BARCODE	
Barcode type:	2D Code (DMC)
Alpha numeric content:	N19B3403A
Spotmark:	No
Spotmark value:	n/a

TRACEABILITY (VERSIONS)		
Vx	Date	Designer
01	06.03.2025	Véronique Savia
02	10.03.2025	Véronique Savia
03	n/a	n/a

COLOURS	
Printed colour(s)	Technical information(s)
Cyan	Keyline
Magenta	
Yellow	
Black	

MERCK

GONAL-f®

150 IU/0.24 mL (11 micrograms/0.24 mL)
300 IU/0.48 mL (22 micrograms/0.48 mL)
450 IU/0.72 mL (33 micrograms/0.72 mL)
900 IU/1.44 mL (66 micrograms/1.44 mL)

1. NAME OF THE MEDICINAL PRODUCT

GONAL-f 150 IU/0.24 mL solution for injection in pre-filled pen.
GONAL-f 300 IU/0.48 mL solution for injection in pre-filled pen.
GONAL-f 450 IU/0.72 mL solution for injection in pre-filled pen.
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 150 IU (equivalent to 11 micrograms) of follitropin alfa* in 0.24 mL solution.
Each pre-filled multidose pen contains 300 IU (equivalent to 22 micrograms) of follitropin alfa* in 0.48 mL solution.
Each pre-filled multidose pen contains 450 IU (equivalent to 33 micrograms) of follitropin alfa* in 0.72 mL solution.
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 a 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.

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

Clinical assessment of GONAL-f indicates that its daily doses, regimens of administration, and treatment monitoring procedures should be individualised to optimise follicular development and to minimise the risk of unwanted ovarian hyperstimulation. It is advised to adhere to the recommended starting doses indicated below.

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.

In the registration trials, a commonly used regimen commenced at 75 to 150 IU FSH daily and was 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.

In clinical practice, the starting dose is typically individualised based on the patient's clinical characteristics, such as markers of ovarian reserve, age, body mass index, and, if applicable, previous ovarian response to ovarian stimulation.

Starting dose

The starting dose can be adjusted in a stepwise manner (a) lower than 75 IU per day if an excessive ovarian response in terms of number of follicles is anticipated based on the patient's clinical profile (age, body mass index, ovarian reserve); or (b) higher than 75 up to a maximum of 150 IU per day may be considered if a low ovarian response is anticipated.

The patient's response should be closely monitored by measuring follicle size and number by ultrasound and/or estrogen secretion.

Dose adjustments

If a patient fails to respond adequately (either low or excessive ovarian response), continuation of that treatment cycle should be evaluated and managed according to the physician's standard of care. In cases of low response, the daily dose should not exceed 225 IU FSH.

If an excessive ovarian response is obtained according to the physician's assessment, 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.

Final follicular maturation

When an optimal ovarian 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.

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

In the registration trials, a commonly used regimen for superovulation involved the administration of 150 to 225 IU of GONAL-f daily, commencing on days 2 or 3 of the cycle.

In clinical practice, the starting dose is typically individualised based on the patient's clinical characteristics, such as markers of ovarian reserve, age, body mass index, and, if applicable, previous ovarian response to ovarian stimulation.

Starting dose

If a low ovarian response is anticipated, the starting dose may be adjusted in a stepwise manner to not higher than 450 IU daily. Conversely, if an excessive ovarian response is expected, the starting dose may be decreased below 150 IU.

The patient's response should continue to be closely monitored by measuring follicle size and number by ultrasound and/or estrogen secretion until adequate follicular development has been achieved.

GONAL-f can be given either alone, or, to prevent premature luteinisation, in combination with a gonadotropin-releasing hormone (GnRH) agonist or antagonist.

Dose adjustments

If a patient fails to respond adequately (either low or excessive ovarian response), continuation of that treatment cycle should be evaluated and managed according to the physician's standard of care. In cases of low response, the daily dose should not exceed 450 IU FSH.

Final follicular maturation

When an optimal response is obtained, 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.

Special population

Elderly population

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 administration. 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 follitropin alfa, FSH or to any of the excipients
- 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

4.4 Special warnings and precautions for use

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 interpatient variability in response to FSH administration, with a poor response to FSH in some patients and exaggerated response in others. The lowest effective dose in relation to the treatment objective should be used.

Porphyria

Patients with porphyria or a family history of porphyria should be closely monitored during treatment with GONAL-f. Deterioration or a first appearance of this condition may require cessation of treatment.

Treatment in women

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

Patients undergoing stimulation of follicular growth, whether 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 oestradiol measurements are recommended to early identify risk factors.

There is evidence to suggest that hCG plays a key role in triggering OHSS and that the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, if signs of ovarian hyperstimulation occur, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or 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.

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of GONAL-f with other medicinal products used to stimulate ovulation (e.g. hCG, clomiphene citrate) may potentiate the follicular response, whereas concurrent use of a GnRH agonist or antagonist to induce pituitary desensitisation may increase the dose of GONAL-f needed to elicit an adequate ovarian response. No other clinically significant medicinal product interaction has been reported during GONAL-f therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no indication for use of GONAL-f during pregnancy. Data on a limited number of exposed pregnancies (less than 300 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of follitropin alfa.

No teratogenic effect has been observed in animal studies (see section 5.3).

In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of GONAL-f.

Breastfeeding

GONAL-f is not indicated during breastfeeding.

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

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).

The following definitions apply to the frequency terminology used hereafter:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1 000 to < 1/100)
Rare (≥ 1/10 000 to < 1/1 000)
Very rare (< 1/10 000)

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)

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.

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 about 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 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:

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

6.4 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.

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.

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.

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 16 needles to be used with the pen for administration.

6.5 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.

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

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

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. HOW TO USE GONAL-f

Always use GONAL-f exactly as your doctor has told you. You should 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 starting dose of GONAL-f is usually individualised and may be adjusted in a stepwise manner.
- The daily dose of GONAL-f should not exceed 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, the continuation of that treatment cycle with GONAL-f should be evaluated and managed accordingly to the standard clinical practice.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see section 2, 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 starting dose of GONAL-f is usually individualized and may be adjusted in a stepwise manner to not higher than 450 IU daily.
- Treatment is continued until your eggs have developed to a desired point. 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.

8. MANUFACTURER

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

9. DATE OF REVISION OF THE TEXT

April 2025 (based on EU SPC approved 06Jan2025)

MERCK

GONAL-f

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GONAL-f

MERCK

N19B3403A

Info-Table – Version 03

IDENTIFICATION OF THE COMPONENT		
Material component code:	N19B3403A	
Local brand:	GONAL-F	
Strength(s):	900 iu	
TECHNICAL DATA		
Packaging site:	Merck Aubonne	
Technical layout ref:	PIL_139x65_V03	
BARCODE		
Barcode type:	2D Code (DMC)	
Alpha numeric content:	N19B3403A	
Spotmark:	No	
Spotmark value:	n/a	
TRACEABILITY (VERSIONS)		
Vx	Date	Designer
01	06.03.2025	Véronique Savia
02	10.03.2025	Véronique Savia
03	n/a	n/a

INSTRUCTIONS FOR USE

GONAL-f® PRE-FILLED PEN
900 IU/1.44 mL

Solution for injection in pre-filled pen
Follitropin alfa

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).
  b. Verify a complete injection (Figure 2).
  c. Read the dose remaining to be injected with a second pen (Figure 3).
- Remove the needle from the pen immediately after each injection.


Fig. 1

Fig. 2

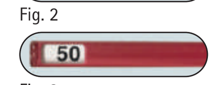


Fig. 3

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 at the end of the Instructions for Use. 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.

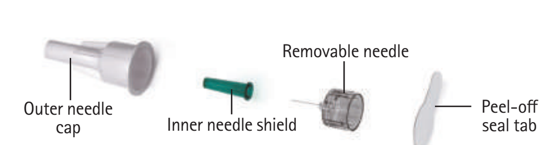
Using your treatment diary to record your daily injection(s) allows you to verify every day that you received the full prescribed dose.

An example of a treatment diary:

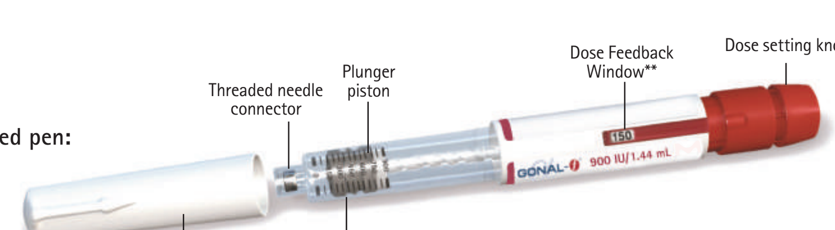
1 Treatment Day Number	2 Date	3 Time	4 Pen Volume 900 IU/1.44 mL	5 Prescribed Dose	6 Dose Feedback Window: Amount Set to Inject	7 Dose Feedback Window: 0	8 Dose Feedback Window: Amount to Be Set for a Second Injection
#1	10/06	07:00	900IU	350	350	☑ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
#2	11/06	07:00	900IU	350	350	☑ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
#3	12/06	07:00	900IU	350	350	☐ if "0", injection complete	☑ if not "0", need second injection Inject this amount .150..using new pen
#3	12/06	07:00	900IU	N/A	150	☑ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen

Get familiar with your GONAL-f® pre-filled pen

Your needle*:



Your pre-filled pen:



*For illustration purposes only. The needles supplied may look slightly different.
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

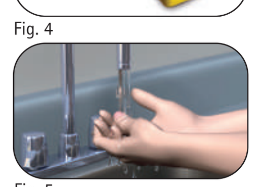


Fig. 5

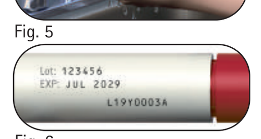


Fig. 6

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).

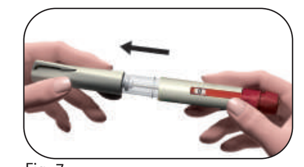


Fig. 7

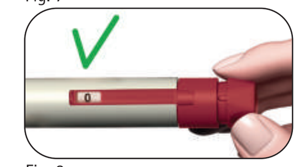


Fig. 8

Choose your injection site:

2.4 Your healthcare provider should show you the injection sites to use around your stomach area (Figure 9). To minimize 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.

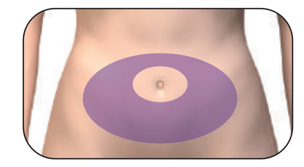


Fig. 9

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).

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 inner needle shield (Figure 16).

Do not recap the needle with the inner needle shield, as it can lead to needle stick injury and infection.


Fig. 10


Fig. 11

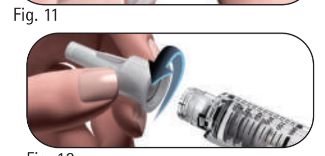


Fig. 12


Fig. 13


Fig. 14

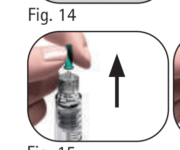


Fig. 15

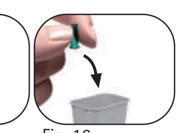


Fig. 16

3.11 Look closely at the tip of the needle for tiny droplet(s) of liquid (Figure 17).

If	Then
Using a new pen	Check for a droplet of liquid at the tip of the needle. • 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 **in the following section** 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**.

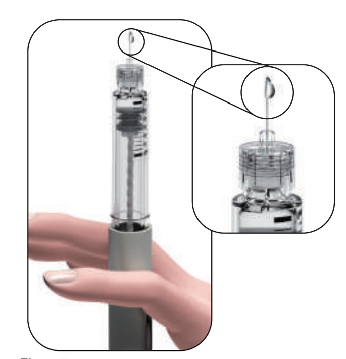


Fig. 17

If you do not see a tiny droplet(s) of liquid at or near the needle tip the first time you use a new pen:

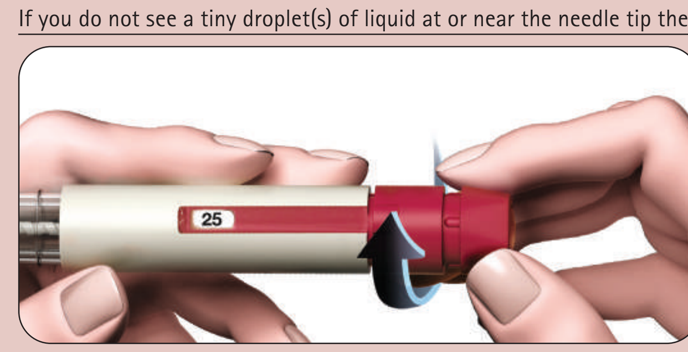


Fig. 18

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

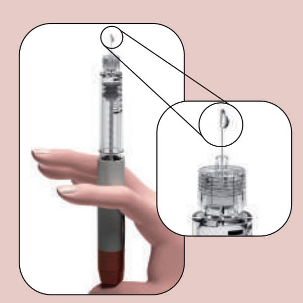


Fig. 20

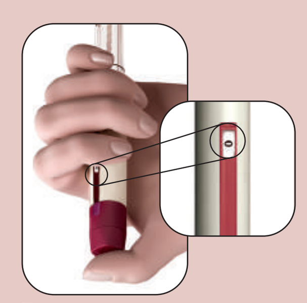


Fig. 21

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.

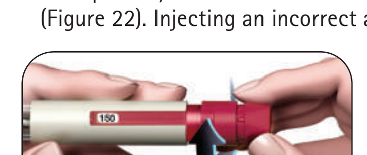


Fig. 22


Fig. 23

- Turn the dose setting knob **forward** to dial up (Figure 22).
- 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).

Note: The larger the dose, the longer it will take to inject.


Fig. 25

5.3 Hold the dose knob down for a minimum of 5 seconds before you remove the needle from your skin (Figure 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.

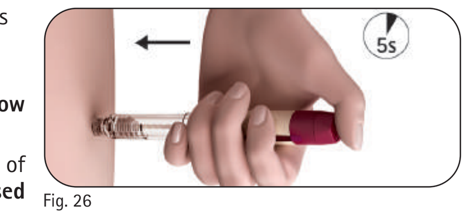


Fig. 26

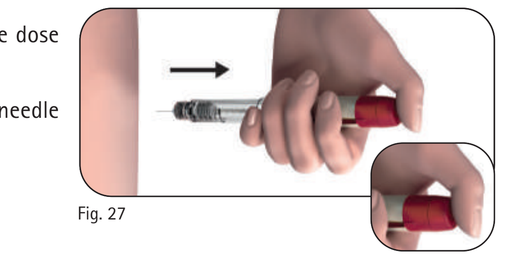


Fig. 27

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).

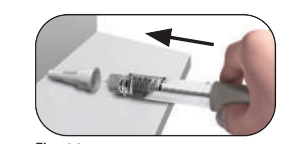


Fig. 28

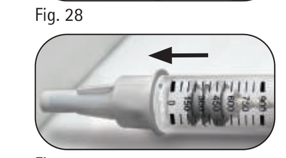


Fig. 29

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.

Do not reuse or share any used needle.

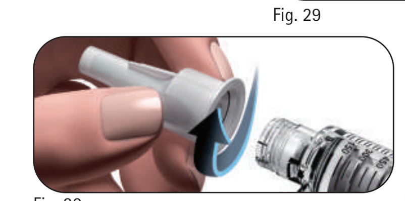


Fig. 30


Fig. 31

Step 7 After the injection

7.1 Check you have given a complete injection:
- Check that the Dose Feedback Window shows "0" (Figure 32).

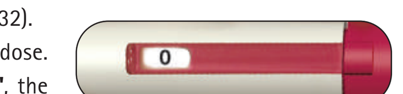


Fig. 32

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.

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.

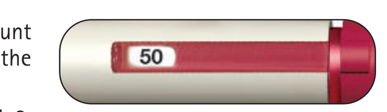


Fig. 33

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.

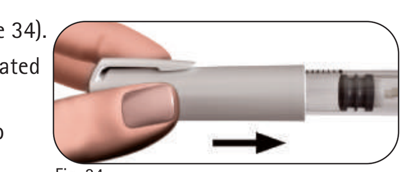


Fig. 34

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 900 IU/1.44 mL	5 Prescribed Dose	6 Dose Feedback Window: Amount Set to Inject	7 Dose Feedback Window: 0	8 Dose Feedback Window: Amount to Be Set for a Second Injection
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen

1 Treatment Day Number	2 Date	3 Time	4 Pen Volume 900 IU/1.44 mL	5 Prescribed Dose	6 Dose Feedback Window: Amount Set to Inject	7 Dose Feedback Window: 0	8 Dose Feedback Window: Amount to Be Set for a Second Injection
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen
	/	:	900IU			☐ if "0", injection complete	☐ if not "0", need second injection Inject this amount ....using new pen

This Instructions for Use has been last revised in: April 2025