

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 that are not ovulating because their 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

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

GONAL-f is not indicated for use in children.

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, OHSS). For the following cycle, your doctor will give you a lower dose of GONAL-f than before.

If you are not ovulating, having no periods and 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 may be performed by placing the sperm into the womb cavity.

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, 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, 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”). 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:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or

Apple App Store

Ireland

HPRA Pharmacovigilance

Website: www.hpra.ie

Malta

ADR Reporting

Website: www.medicinesauthority.gov.mt/adrportal

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, concentrated phosphoric acid and sodium hydroxide.
- 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 12/2019.

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

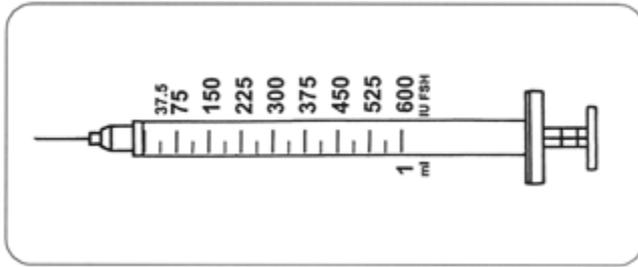
- This section tells you how to prepare and use your GONAL-f powder and solvent.
- Before starting the preparation, please read these instructions the whole way through first.
- Give yourself the injection at the same time each day.

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.

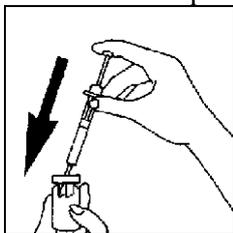
2. Get together everything you need and lay them out:

- 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

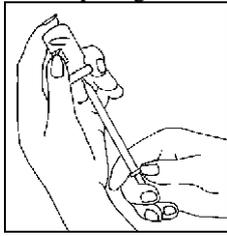
- Remove the protective caps from the powder vial and from the pre-filled syringe.
- Take your pre-filled syringe, insert the needle into the powder vial and slowly inject all the solvent into the vial containing the powder.
- Remove the syringe from the vial and throw it away (put the protective cap 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

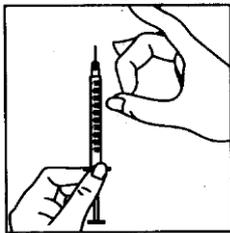
- Swirl gently the vial of GONAL-f prepared in step 3, do not shake. Check that the solution is clear and does not contain any particles.
- Take the syringe for injection and fill it with air by pulling the plunger to the correct dose in International Units (IU FSH).
- Insert the needle into the vial,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



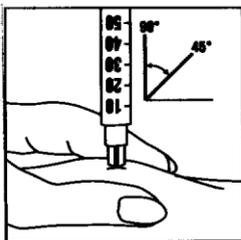
5. Removing air bubbles

- 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.