

**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS'
REGULATIONS (PREPARATIONS) - 1986**

This medicine is dispensed with a doctor's prescription only



**Solution for injection in a pre-filled pen
For subcutaneous injection**

Active ingredient: Follitropin Alfa 600 IU*/1 mL (44 mcg/1 mL)

Available in the following doses:

GONAL-f® 300 IU/0.5 mL

GONAL-f® 450 IU/0.75 mL

GONAL-f® 900 IU/1.5 mL

(*IU – international units)

Inactive ingredients and allergens in this medicine – see section 6.

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist. Keep this leaflet at hand; you may need to read it again.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems that their medical condition is similar.

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.

1. WHAT IS THE MEDICINE INTENDED FOR

GONAL-f is a medicine that contains follitropin alfa. This is a type of Follicle Stimulating Hormone (FSH) which belongs to the family of hormones called “gonadotropins” that are involved in reproduction and fertility. Follitropin alfa is generated using genetic engineering technology.

GONAL-f is used for the following situations:

In women:

- To help in release of an egg from the ovary (ovulation) in women who cannot ovulate and who have not responded to treatment with a medicine called “clomiphene citrate”.
- In combination with another medicine called “lutropin alfa” (luteinizing hormone or LH) - to help release an egg from the ovary (ovulation) in women who do not ovulate because their bodies produce very little gonadotropins (FSH and LH).
- To help in the development of several follicles (which contain eggs) in women undergoing fertility treatments (a procedure that helps you to become pregnant), such as in vitro fertilization, gamete intrafallopian transfer or zygote intrafallopian transfer.

In men:

- In combination with an additional medicine called human Chorionic Gonadotropin (hCG) – to promote sperm production in men who are infertile due to a low level of certain hormones.

Therapeutic group: Gonadotropins.

2. BEFORE USING THE MEDICINE

You and your partner in the fertility process must be evaluated before starting the treatment by a doctor specializing in treating fertility disorders.

Do not use the medicine:

- if you have a sensitivity (allergy) 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 one of the following conditions:

- you are pregnant or breastfeeding.
- enlarged ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
- unexplained vaginal bleeding.
- breast cancer, uterine cancer or ovarian cancer.
- a condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), or reproductive organ defects.

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 commencing use.

Special warnings regarding use of this medicine

Porphyria

Tell your doctor before you start treatment, if you know that you or any member of your family have porphyria (a metabolic disease manifested by an inability to break down porphyrins). This is a disease that can be hereditary.

Tell your doctor straight away if:

- you notice that your skin becomes fragile and easily blistered, especially skin that is frequently in the sun, and/or
- you have stomach, arm or leg pain.

In case of the above events, the doctor may recommend that you stop treatment.

Ovarian Hyper-Stimulation Syndrome (OHSS)

In women, this medicine increases the risk of developing OHSS. This condition is characterized by overdevelopment of the follicles and formation of large cysts. If you get lower abdominal pain, gain weight rapidly, feel sick or are vomiting or if you have difficulty in breathing, talk to your doctor straight away; the doctor might ask you to stop using the medicine (see section 4).

In case you are not ovulating, and if the recommended treatment regimen is adhered to, the occurrence of OHSS is less likely. GONAL-f treatment seldom causes severe OHSS, unless it is administered with a medicine for final follicular maturation (containing human Chorionic Gonadotropin, hCG). In the event of development of OHSS, your doctor may not give you any medicine for final follicular maturation and for induction of ovulation (hCG) in this treatment cycle and will tell you not to have sex or will recommend using a barrier contraceptive method (e.g., condom), to prevent pregnancy, for at least four days.

Multiple pregnancy

When using GONAL-f, the risk of multiple pregnancy, mostly twins, increases, compared to a natural pregnancy. Multiple pregnancy may lead to medical complications for you and your babies. You can reduce the risk of multiple pregnancy by using the appropriate dose of GONAL-f and the recommended treatment regimen. When undergoing assisted reproductive technology, the risk of having a multiple pregnancy depends on your age, the quality and the number of fertilized eggs or the number of embryos placed inside the uterus.

Miscarriage

When undergoing assisted reproductive technology or stimulation of your ovaries to produce eggs, the chance of a miscarriage increases in comparison to a woman with a natural pregnancy.

Blood clotting problems (thromboembolic events)

If you have suffered in the past or recently from blood clots in the leg or in the lung, or had a heart attack or stroke, or if these happened to one of your family members, then you might have a higher risk of these problems occurring or becoming 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 is usually not effective in these cases.

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

Children and adolescents

GONAL-f is not indicated for use in children and adolescents under 18 years of age.

Drug interactions

If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. In particular if you are taking:

- other medicines used to help ovulation (such as clomiphene citrate or hCG). Taking these medicines with GONAL-f may increase the response of your follicles.
- Gonadotropin-releasing hormone (GnRH) agonist or antagonist. These medicines reduce your sex hormone levels and cause cessation of ovulation, which may increase the required dosage of GONAL-f to produce follicles.

Pregnancy and breastfeeding

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

Driving and operating machinery

This medicine is not expected to affect your ability to drive or operate machinery.

Important information regarding some of the ingredients of the medicine

- GONAL-f contains less than 1 mmol (23 mg) sodium per dose – considered “sodium-free”.
- GONAL-f contains 60 mg sucrose per ml.

3. HOW SHOULD YOU USE THE MEDICINE

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about your dose or about how to take this medicine.

Using the medicine

The medicine is intended for subcutaneous injection. The pre-filled pen can be used for several injections.

- The first injection of GONAL-f should be given under medical supervision.
- Your doctor or nurse will show you how to use GONAL-f to inject the medicine.
- If you inject GONAL-f to yourself, please carefully read and follow the “Injection Instructions”.

Dosage

The dosage and treatment regimen will be determined by the doctor only. Below is the recommended dosage per indication.

The dosages are stated in International Units (IU) and milliliters (mL).

Women

Women who 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 treatment within the first 7 days of your menstrual cycle. If you do not have periods, start using the medicine on any convenient day.
- The usual starting dose of GONAL-f is 75-150 IU (0.12-0.24 mL) 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 will usually not be higher than 225 IU (0.36 mL).
- When you get the desired response, you will be given an additional single injection of 250 micrograms of recombinant hCG (r-hCG is a chorionic hormone made in a laboratory using genetic engineering technology), or a dose of 5,000-10,000 IU of hCG, administered 24-48 hours after your last GONAL-f injection. It is recommended to have sex 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 to the treatment (Ovarian Hyper-Stimulation Syndrome, see section 2 OHSS), your treatment will be stopped and you will not be given the hCG dose. For the following treatment cycle, your doctor will prescribe you a lower dose of GONAL-f than before.

Women who are not ovulating and have no periods, who have been diagnosed with very low levels of FSH and LH:

- The usual starting dose of GONAL-f is 75-150 IU (0.12-0.24 mL) together with 75 IU (0.12 mL) of lutropin alfa.
- Inject both 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 an additional single injection of 250 micrograms of recombinant hCG (r-hCG is a chorionic hormone made in a laboratory using genetic engineering technology), or a dose of 5,000-10,000 IU of hCG administered within 24-48 hours after your last injection of GONAL-f and lutropin alfa. It is recommended to have sex 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 desired response after 5 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 to the treatment (Ovarian Hyper-Stimulation Syndrome, see section 2 OHSS), your treatment will be stopped, including hCG administration. For your following treatment cycle, your doctor will prescribe you a lower dose of GONAL-f than before.

Women who need maturation stimulation of several eggs for collection prior to any assisted reproductive technology:

- The usual starting dose of GONAL-f is 150-225 IU (0.24-0.36 mL) each day, from day 2 or 3 of your treatment cycle.
- The GONAL-f dose may be increased, depending on your response. The maximum daily dose is 450 IU (0.72 mL).
- Treatment is continued until your eggs have developed to a desired point. This usually occurs within 10 days, but can take any time between 5-20 days. Your doctor will monitor by performing blood tests and/or an ultrasound to check when this occurs.
- When your eggs are ready, you will be given an additional single injection of 250 micrograms of recombinant hCG (r-hCG is a chorionic hormone made in a laboratory using genetic engineering technology), or a dose of 5,000-10,000 IU of hCG, administered 24-48 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. GONAL-f treatment will be started approximately two weeks after starting treatment with the agonist preparation. Continue with the combined treatment of the two preparations until reaching the desired maturation of the follicles. For example, after two weeks of GnRH agonist treatment, a dosage of 150-225 IU GONAL-f is administered for 7 days. The dose is adjusted according to your ovarian response.

Men

- The usual dose of GONAL-f is 150 IU (0.24 mL), administered together with hCG.
- This combination treatment will be administered three times a week for at least 4 months.
- In the event of no response to treatment after 4 months, your doctor may suggest that you continue using the combined treatment for at least 18 months.

Do not exceed the recommended dose

If you accidentally took a higher dosage

The effect of taking too much GONAL-f is unknown, although Ovarian Hyper-Stimulation Syndrome (OHSS) can be expected to occur, as described in section 4. However, OHSS will only occur if hCG is also administered (see section 2 OHSS).

If you forget to take the medicine

If you forget to take this medicine at the scheduled time, do not take a double dose. Take the next dose at the usual time and consult your doctor.

Even if there is an improvement in your health, do not stop treatment with this medicine without consulting the doctor or pharmacist.

Adhere to the treatment regimen recommended by the doctor.

Do not take medicines in the dark! Check the label and dose each time you take medicine. Wear glasses if you need them.

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

4. SIDE EFFECTS

As with any medicine, use of GONAL-f may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Serious side effects in women:

- Lower abdominal pain together with nausea and vomiting; these effects may result from Ovarian Hyper-Stimulation Syndrome (OHSS). This may indicate that the ovaries overreacted to the treatment and that large ovarian cysts developed (see also section 2 under "OHSS"). This side effect is common (may occur in 1 out of 10 patients).
- OHSS may become severe when there is significant enlargement of the 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 occur in 1 out of 100 patients).
- Complications of OHSS such as twisting of ovaries or formation of blood clots. These effects are rare (may occur in 1 out of 1,000 patients).
- Serious blood clotting complications (thromboembolic events), sometimes independent of OHSS. These complications may cause chest pain, breathlessness, stroke or heart attack (see also section 2 under "Blood clotting problems"). These effects are very rare (may occur in 1 out of 10,000 patients).

Serious side effects in men and women:

- Allergic reactions such as rash, red skin, hives and swelling of the face with difficulty breathing can sometimes be serious. This side effect is very rare (may occur in 1 out of 10,000 patients).

If you notice any of the above-mentioned side effects, you should immediately contact a doctor; he might stop your GONAL-f treatment.

Other side effects in women:

Very common (may occur in more than 1 out of 10 patients)

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

Common (may occur in 1 out of 10 patients)

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

Very rare (may occur in 1 out of 10,000 patients)

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

Other side effects in men:

Very common (may occur in more than 1 out of 10 patients)

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

Common (may occur in 1 out of 10 patients)

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

Very rare (may occur in 1 out of 10,000 patients)

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

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects:

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: <https://sideeffects.health.gov.il>

5. HOW SHOULD THE MEDICINE BE STORED

- Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the cartridge label and package. The expiry date refers to the last day of that month.
- Store refrigerated at a temperature of between 2°C-8°C. Do not freeze.
- Within its shelf-life, this product may be stored unopened below 25°C for up to 3 months. Do not return it to the refrigerator. After this date, discard it, even if you did not use it.
- Keep in the original package to protect from light.
- Do not use the medicine if you notice that the solution is not clear or contains particles or if the product has been damaged.
- It is recommended to record the date of first use on the GONAL-f pre-filled pen.
- After opening, the product can be stored below 25°C for up to 28 days only. After 28 days from the date of opening, discard it.
- Do not throw away medicines via the sewage system or household waste. Ask the pharmacist how to dispose of medicines you no longer need. These measures will help protect the environment.

6. FURTHER INFORMATION

What the medicine contains

- The active substance is follitropin alfa
- There are 600 IU (44 micrograms) of follitropin alfa in each milliliter of solution.
The pre-filled pen is provided in the following dosages:
300 IU/0.5 mL (22 micrograms)
450 IU/0.75 mL (33 micrograms)
900 IU/1.5 mL (66 micrograms)

- In addition to the active ingredient, the medicine also contains – Sucrose, m-cresol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, Poloxamer 188, L-methionine, concentrated phosphoric acid, sodium hydroxide and water for injection

What the medicine looks like and the contents of the pack

- GONAL-f is presented as a clear, colourless solution in a pre-filled pen for injection.
- The pack contains 1 pre-filled pen and disposable needles.

Registration holder's name and address: Merck Serono Ltd., 18 Ha'kishon St., Yavne 81220

Manufacturer's name and address: Merck Europe B.V., Amsterdam, the Netherlands

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 131 55 31061 00

This leaflet was revised in May 2021 according to the MOH guidelines.