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

The medicine is dispensed with a doctor's prescription only

# PERGOVERIS® Pre-filled pen
## Solution for Subcutaneous Injection

**Active ingredients:**
Follitropin Alfa (r-hFSH)
Lutropin Alfa (r-hLH)

Provided in three volumes:
**Pergoveris (300 IU* r-hFSH + 150 IU r-hLH)/0.48 mL**
**Pergoveris (450 IU r-hFSH + 225 IU r-hLH)/0.72 mL**
**Pergoveris (900 IU r-hFSH + 450 IU r-hLH)/1.44 mL**
(*IU – international units)

Inactive and allergenic ingredients in the preparation – 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; 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 to you that their medical condition is similar.
The medicine is not intended for girls and adolescent girls below the age of 18.

## 1. WHAT IS THE MEDICINE INTENDED FOR

The medicine is intended for stimulation of follicles and their maturation in the ovaries in adult women with severe gonadotropin hormone deficiency (FSH and LH).
In clinical trials, patients were defined by levels of LH (the luteinizing hormone) in the blood, below 1.2 international units per liter.

**Therapeutic group:** Gonadotropin hormones that are involved in regulating the reproductive system.

The medicine contains 2 active ingredients called Follitropin Alfa and Lutropin Alfa. Both ingredients belong to a group of hormones called gonadotropins that are involved in regulation of the reproductive system.

The active ingredients in the medicine are copies of the natural hormones, FSH and LH in the body:
FSH, follicle stimulating hormone - stimulates maturation of eggs.
LH, luteinizing hormone - stimulates release of the eggs.

The medicine allows women with low levels of FSH and LH to develop a follicle. The injection of another hormone - human chorionic gonadotropin (hCG) - leads to the release of the egg from the follicle.
This process helps to achieve pregnancy.

## 2. BEFORE USING THE MEDICINE

You and your partner to the fertility process must be examined by a doctor specializing in fertility problems before commencing treatment.

**Do not use this medicine if:**

- you are sensitive (allergic) to the active ingredients (FSH and/or LH) or to any of the additional ingredients contained in the medicine (for a list of the inactive ingredients, see section 6).
- you are suffering from a brain tumor (in the hypothalamus or in the pituitary gland [hypophysis]).
- you are suffering from enlarged ovaries or sacs of fluid within the ovaries (ovarian cysts) of unknown origin.
- you are suffering from unexplained vaginal bleeding.
- you have ovarian, uterine or breast cancer.
- you are suffering from a condition that makes normal pregnancy impossible, e.g., early menopause, sex organ defect (malformation) or a benign uterine tumor.

Do not use the medicine if any of the above conditions apply to you. If you are unsure, consult a doctor, pharmacist or nurse before using the medicine.

**Special warnings regarding use of the medicine**
Talk to the doctor, pharmacist or nurse before using Pergoveris.

Porphyria
Talk to your doctor before commencing treatment if you or any of your family members have porphyria (a hereditary disease in which there is no ability to break down porphyrins).

**Tell your doctor immediately if:**
- Your skin becomes fragile and easily blistered, especially after frequent exposure to sunlight.
- You have stomach, arm or leg pain.

In these cases, the doctor may recommend stopping treatment.

Ovarian hyperstimulation syndrome (OHSS)
This medicine stimulates the ovaries and increases the risk of developing a condition called ovarian hyperstimulation syndrome (OHSS). In this condition, your follicles develop too much and become large cysts. If you are suffering from lower abdominal pains, rapid weight gain, nausea, vomiting or if you have breathing difficulties, refer to the doctor immediately. Your doctor might instruct you to stop using this medicine (see section 4, under "Most serious side effects").

In case you are not ovulating and you adhere to the recommended treatment dose and schedule of administration, the risk of severe OHSS is less likely. Pergoveris treatment seldom causes severe OHSS. The risk of onset of this syndrome increases when using a medicine for final follicular maturation (which contains human chorionic gonadotropin - hCG) - see section 3 under “Dosage". If you are developing OHSS, your doctor may not treat you with hCG in this treatment cycle and will ask you not to have sex or will ask you to use a barrier contraceptive method for at least 4 days.

Your doctor will carefully monitor the ovarian response, based on ultrasound and blood tests (estradiol levels) before and during the treatment cycle.

Multiple pregnancy
When using Pergoveris, there is a higher risk of pregnancy with more than one fetus ("multiple pregnancy", mostly twins), compared to a pregnancy resulting from natural conception. 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 Pergoveris and by administration at the right times.
To minimize the risk of multiple pregnancy, ultrasound scans as well as blood tests are recommended.

Miscarriage
When undergoing stimulation of the ovaries to produce eggs, the risk of miscarriage is higher than in the average population.

Ectopic pregnancy
Women who have a history of blocked or damaged fallopian tubes (tubal disease) are at risk of pregnancy in which the fetus implants outside the womb (ectopic pregnancy), in both spontaneous pregnancy and pregnancy following fertility treatments.

Blood clotting problems (thromboembolic events: thromboembolism)
Consult the doctor before using the medicine if you or a member of your family have ever had blood clots in the leg or in the lung, or a heart attack or stroke. You may be at a higher risk of serious blood clots or of worsening of existing clots during treatment with Pergoveris.

Tumors of sex organs
There have been reports of tumors in the ovaries and other sex organs, both benign and malignant, in women who have undergone multiple regimens for infertility treatment.

Allergic reactions
There have been isolated reports of non-serious allergic reactions to Pergoveris. If you have ever had this effect with a similar medicine, inform the doctor before using Pergoveris.

**Girls and adolescent girls**
Pergoveris is not intended for use in girls and adolescent girls below the age of 18.

**Drug interactions**
**If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.**
Do not administer Pergoveris with other medical preparations mixed in the same injection.
Pergoveris can be used with a follitropin alfa (FSH) preparation, as separate injections, if prescribed for you by the doctor.

**Pregnancy and breastfeeding**
Do not use Pergoveris if you are pregnant or breastfeeding.

**Driving and operating machinery**
This medicine is not expected to affect your ability to drive or operate dangerous machines.

**Important information about some of the ingredients in this medicine**
Pergoveris contains less than 1 mmol (23 mg) sodium per dose – considered "sodium-free".

Pergoveris (300 IU + 150 IU)/0.48 mL contains 0.176 mg sodium.
Pergoveris (450 IU + 225 IU)/0.72 mL contains 0.263 mg sodium.
Pergoveris (900 IU + 450 IU)/1.44 mL contains 0.527 mg sodium.

## 3. HOW TO USE THE MEDICINE

Always use this medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about your dose or about how to take this medicine.

**Using the medicine**
- Pergoveris is intended to be given by injection under the skin. In order to reduce skin irritation, select a different injection site each day.
- The doctor or nurse will show you how to use the Pergoveris pre-filled pen to inject the medicine.
- Once they confirm that you are able to administer the medicine safely, you can then prepare and inject the medicine yourself at home.
- When you self-inject, carefully read and follow the "Instructions for use" booklet attached to the package.

**Dosage**
The dosage and treatment regimen will be determined by the doctor only.

A treatment regimen commences with the recommended dosage of Pergoveris containing 150 IU of follitropin alfa and 75 IU of lutropin alfa every day.
- According to your response, your doctor may decide to add a dose of a follitropin alfa preparation every day in addition to your Pergoveris injection. In this case, the follitropin alfa dosage is usually increased every 7 or every 14 days by 37.5-75 IU.
- Treatment is continued until the desired response is achieved. This is when you have developed a suitable follicle, as confirmed by ultrasound scans and blood tests.
- This may take up to 5 weeks.

When the desired response is achieved, you will be given a single injection of human chorionic gonadotropin (hCG) 24-48 hours after the last Pergoveris injection. It is recommended to have sex on the day of the hCG injection and on the following day. Alternatively, intrauterine insemination (IUI) can be performed or assistive reproductive technologies (ART) used.

If your body responds too strongly, the treatment will be stopped and human chorionic gonadotropin (hCG) will not be given (see section 2, under "Ovarian hyperstimulation syndrome"). In this case, your doctor will prescribe you a lower dose of follitropin alfa in the following treatment cycle.

**Do not exceed the recommended dose.**

**How to use Pergoveris pre-filled pen**
See the "Instructions for use" booklet enclosed to the package.

**If you accidentally took a higher dosage**
The effects of an overdose of Pergoveris are unknown, nevertheless, ovarian hyperstimulation syndrome (OHSS) may occur. However, this will only occur if human

chorionic gonadotropin (hCG) is administered (see section 2, under “Ovarian hyperstimulation syndrome”).

If you took an overdose, or if a child has accidentally swallowed some medicine, refer immediately to a doctor or proceed to a hospital emergency room, and bring the package of the medicine with you.

**If you forget to take the medicine**
Do not take a double dose to compensate for a forgotten dose. Contact your doctor.

Adhere to the treatment regimen recommended by the doctor.

**Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take the medicine. Wear glasses if you need them.**
**If you have further questions regarding use of the medicine, consult the doctor, pharmacist or nurse.**

## 4. SIDE EFFECTS

As with any medicine, use of Pergoveris may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

**Most serious side effects**
**Contact the doctor immediately if you notice any of the side effects detailed below. The doctor might ask you to stop using Pergoveris.**

<u>Allergic reactions</u>
Allergic reactions such as rash, skin redness, hives, swelling of the face with breathing difficulties, which sometimes can be serious. This side effect is very rare.

<u>Ovarian Hyperstimulation Syndrome (OHSS)</u>
- Lower abdominal pain together with nausea or vomiting, may be the symptoms of OHSS. This may indicate an over-reaction of the ovaries to the treatment and development of sacs of fluid or cysts (see section 2, under “Ovarian hyperstimulation syndrome”). This side effect is common. If this effect occurs, the doctor will need to examine you as soon as possible.
- OHSS may become severe when there is significant enlargement of the ovaries, decreased urine production, weight gain, breathing difficulties and/or possible fluid accumulation in the stomach or chest. This side effect is uncommon (may affect up to 1 in 100 patients).
- Complications of OHSS, e.g., twisting of ovaries or development of blood clots are rare (may affect up to 1 in 1,000 patients).
- Serious blood clotting complications (thromboembolic events), usually with severe OHSS, are very rare. This complication could cause chest pain, breathlessness, stroke or heart attack. In rare cases, this can also happen independently of OHSS (see section 2, under “Blood clotting problems [thromboembolic events: thromboembolism]“).

**Additional side effects**

<u>Very common</u> (may affect more than 1 in 10 patients):
- sacs of fluid within the ovaries (ovarian cysts)
- headache

- local reactions at the injection site such as pain, itching, bruising, swelling or irritation

Common (may affect up to 1 in 10 patients):
- diarrhea
- chest pain
- nausea and vomiting
- abdominal or pelvic pain
- abdominal cramps or bloating

Very rare (may affect up to 1 in 10,000 patients):
- your asthma may worsen

**If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in this leaflet, consult with the doctor.**

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 TO STORE THE MEDICINE

- Avoid poisoning! This medicine, and any other medicine, must 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 package. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C-8°C). Do not freeze. Protect from light.
- After first opening, the pre-filled pen can be stored outside of the refrigerator (at 25°C) for a period of up to 28 days.
- Do not use the preparation if you notice that the preparation has been damaged, if the solution is not clear or contains particles. Do not use the medicine remaining in the pre-filled pen after 28 days.
- After injecting, safely discard the used needle.
- Do not discard medicines into the sewage drainage system or household waste. Ask the pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

## 6. FURTHER INFORMATION

**What the medicine contains**
The active ingredients are follitropin alfa and lutropin alfa
- Each Pergoveris pen (300 IU + 150 IU)/0.48 mL contains 300 IU of follitropin alfa and 150 IU of lutropin alfa in 0.48 mL and can supply two doses of Pergoveris 150 IU/75 IU.
- Each Pergoveris pen (450 IU + 225 IU)/0.72 mL contains 450 IU of follitropin alfa and 225 IU of lutropin alfa in 0.72 mL and can supply three doses of Pergoveris 150 IU/75 IU.
- Each Pergoveris pen (900 IU + 450 IU)/1.44 mL contains 900 IU of follitropin alfa and 450 IU of lutropin alfa in 1.44 mL and can supply six doses of Pergoveris 150 IU/75 IU.

**In addition to the active ingredients, the medicine also contains:**
Sucrose, L-arginine monohydrochloride, poloxamer 188, L-Methionine, phenol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, water for injection.

Tiny amounts of concentrated phosphoric acid and sodium hydroxide are added to maintain a normal acidity level (pH).

**What the medicine looks like and the contents of the package -**
Pergoveris is provided as a clear, colorless to light yellow solution for injection, in a multi-dose pre-filled pen:

- Pergoveris (300 IU + 150 IU)/0.48 mL comes in a package which includes one multi-dose pre-filled pen and 5 disposable injection needles.
- Pergoveris (450 IU + 225 IU)/0.72 mL comes in a package which includes one multi-dose pre-filled pen and 7 disposable injection needles.
- Pergoveris (900 IU + 450 IU)/1.44 mL comes in a package which includes one multi-dose pre-filled pen and 14 disposable injection needles.

**License holder and address:** Merck Serono Ltd., 18 Hakishon St., Yavne 81220

**Manufacturer and address:** Merck Europe B.V., Amsterdam, The Netherlands

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**Registration number of the medicine in the National Drug Registry of the Ministry of Health:** 160 56 35355 00