PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE
PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986
The medicine is dispensed with a doctor's prescription only

Luveris® 75 IU (International Units)

Powder and solvent for solution for SC injection
Powder in a vial
Solvent in a vial

Active ingredient: Lutropin alfa 75 IU/ML
Solvent: Water for injection
Inactive ingredients: see section 6 and section 2 under "Important information regarding some of the ingredients of the medicine".

Read this leaflet carefully in its entirety before using the medicine.
- This leaflet contains concise information about the medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, refer to the doctor or pharmacist.
- This medicine has been prescribed for the treatment of your medical condition. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.
- If a side effect occurs, if one of the side effects worsens, or if you notice a side effect not mentioned in this leaflet, refer to your doctor or pharmacist. See section 4.

1. WHAT IS THE MEDICINE INTENDED FOR

What is Luveris 75 IU
Luveris 75 IU is a preparation containing lutropin alfa, a recombinant Luteinising Hormone (LH), which is essentially similar to the hormone found naturally in the human body, and is produced by means of biotechnology. It belongs to the family of hormones called gonadotropins, which are involved in the control of the reproductive process.

What is Luveris 75 IU used for
Luveris 75 IU is recommended for the treatment of adult women who produce very low levels of the hormones involved in the natural reproductive cycle.
Luveris 75 IU is administered together with another hormone called Follicle Stimulating Hormone (FSH), to bring about the development of follicles which are in the ovary, and maturation of the eggs (ova) in it.
This process is followed by treatment with a single dose of human Chorionic Gonadotropin (hCG), which leads to the release of the egg from the follicle (ovulation).

Therapeutic group: Gonadotropic hormone which is involved in the control of the reproductive system.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:
- You are allergic (hypersensitive) to gonadotropins (such as: luteinising hormone, follicle stimulating hormone or human chorionic gonadotropin), or to any of the additional ingredients contained in Luveris 75 IU (see section 6).
- You have ovarian, uterine or breast cancer.
- You have been diagnosed with a brain tumour.
- You have ovarian enlargement or sacs of fluid within the ovaries (ovarian cyst) of unknown origin.
- You have unexplained vaginal bleeding.

Do not use Luveris 75 IU if any of the above-mentioned cases applies to you. If you are not sure, consult your doctor or pharmacist before using this medicine.

Special warnings regarding use of the medicine
Refer to your doctor, pharmacist or nurse before using Luveris 75 IU.
You and your fertility partner should undergo fertility tests before the treatment is started.
It is recommended not to use Luveris 75 IU in cases in which a normal pregnancy is impossible, such as nonfunctional ovaries due to a condition called primary ovarian failure, or malformations of sex organs.

Porphyria
Tell your doctor before starting treatment if you or any member of your family have porphyria (an inherited disease that may be passed on from parents to children, in which porphyrins are not broken down).

Ovarian hyperstimulation syndrome (OHSS)
This medicine stimulates your ovaries. This increases the risk of developing ovarian hyperstimulation syndrome (OHSS). Namely, your follicles develop too much and become large cysts. If you experience lower abdominal pain, rapid weight gain, nausea, vomiting or if you have difficulty breathing, refer to a doctor straight away who might instruct you to stop using this medicine (see section 4 under "Serious side effects").
In case you are not ovulating, and if the recommended dose and schedule of administration are adhered to, the occurrence of OHSS is lower. Luveris 75 IU treatment seldom causes severe OHSS, unless a medicine for final follicular maturation (containing human Chorionic Gonadotropin – hCG) is used (see section 3 under "How much to use").
If you develop OHSS, your doctor may not give you hCG in this treatment cycle and ask you **not** to have sexual intercourse or ask you to use barrier contraceptive methods for at least 4 days.
Your doctor will monitor ovarian response, based on ultrasound and a blood test before and during the course of treatment.

Multiple pregnancy
When using Luveris 75 IU, there is a higher risk of being pregnant with more than one embryo ("multiple pregnancy", mostly twins), than when conceiving 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 Luveris 75 IU and by administration at the right times. When using assisted reproductive technologies, 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 using assisted reproductive technologies or upon stimulation of your ovaries to produce eggs, the chance of having a miscarriage is higher than the average woman.

Ectopic pregnancy
Women with a history of tubal diseases are at a higher risk of ectopic pregnancy (a pregnancy in which the embryo is implanted outside the womb), whether the pregnancy is obtained by spontaneous conception or with fertility treatments.

Blood clotting problems (thromboembolic events: thromboembolism)
Refer to a doctor before using Luveris 75 IU if you or any of your family members have ever had blood clots in the leg or in the lung, or a heart attack or stroke. You might be at higher risk of developing severe blood clots or existing blood clots may become worse with Luveris 75 IU treatment.

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

Birth defects
Birth defects after use of assisted reproductive technologies may be slightly higher than after spontaneous conceptions. This could be due to differences in parental factors such as maternal age, genetics, as well as the assisted reproductive technology procedures and multiple pregnancy.

Children and adolescents
Luveris 75 IU is not intended 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.
Do not use Luveris 75 IU as a mixture with other medicines in the same injection, except for follitropin alfa, if it has been prescribed for you by the doctor.

Pregnancy and breast-feeding
Do not use Luveris 75 IU if you are pregnant or breast-feeding. If you are pregnant or breast-feeding, consult with the doctor or pharmacist before using medicines.

Driving and using machines
Luveris 75 IU has no or negligible influence on the ability to drive and use machines.

Important information regarding some of the ingredients of the medicine
Luveris 75 IU contains less than 1 mmol sodium (23 mg) per dose of 75 IU; it is defined as "sodium-free".
Luveris 75 IU contains 47.75 mg sucrose in 1 ml.

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 the medicine dosage and treatment regimen.

Using this medicine
Your doctor will decide on the dose and schedule of administration most appropriate for you during this course of treatment.

How much to use
Luveris 75 IU is usually used every day for up to 3 weeks, simultaneously with injections of FSH.
- **The usual starting dose** is 75 IU (1 vial) of Luveris together with 75 IU or 150 IU of FSH.
- **According to your response,** the doctor may increase the dose of FSH, preferably by a dosage of 37.5-75 IU at 7-14-day intervals.

Your doctor may extend the treatment up to 5 weeks.
When the desired response has been obtained, a single injection of human Chorionic Gonadotropin – hCG is given within 24 to 48 hours after the last injection of Luveris 75 IU and FSH. It is recommended to have sexual intercourse on the day of, and the day following, administration of the hCG injection. Alternatively, Intra-Uterine Insemination (IUI) may be performed.
If an excessive response is obtained, treatment should be stopped and hCG withheld (see section 4 under "Ovarian hyperstimulation syndrome"). In the following treatment cycle, your doctor will prescribe a lower dose of FSH than that of the previous treatment cycle.

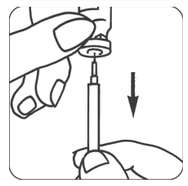
Do not exceed the recommended dose.

Method of administration
Luveris 75 IU is intended for subcutaneous use, which means injection under the skin. Each vial is for single use only.

If you self-inject Luveris 75 IU, read these instructions carefully:
- Wash your hands. It is important that your hands and all the items you use be as clean as possible.
- Assemble all the necessary items. Lay out everything on a clean surface:
  - one vial of Luveris 75 IU
  - one vial of solvent
  - two alcohol swabs
  - one syringe
  - one reconstitution (mixing) needle for dissolving the powder in the solvent
  - a fine-bore needle for subcutaneous injection
  - a safe sharps container for disposal of glass and needles
- Remove the protective cap **from the solvent vial**.
  Attach the **reconstitution needle** to the syringe and draw up some air into the syringe by pulling the plunger to approximately the 1 ml mark. Insert the needle into the vial, push the plunger to expel the air, turn the vial upside down and gently draw up all the solvent.
  Set the syringe down carefully on the work surface, taking care not to touch the needle.

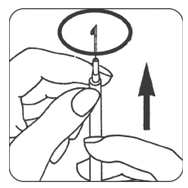
- Prepare the injection solution: Remove the protective cap **from the Luveris 75 IU powder vial**, pick up the syringe and slowly inject the solvent into the vial of Luveris 75 IU. Swirl gently without removing the syringe. **Do not shake**.

- After the powder has dissolved (which usually occurs immediately), check that the solution is clear and does not contain any particles. Now, turn the vial upside down and gently draw the solution back into the syringe.

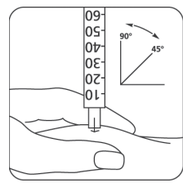


Luveris 75 IU and follitropin alfa powder can be mixed, instead of injecting each preparation separately. Follow the following instructions for injection of the 2 preparations together: after dissolving the Luveris 75 IU powder, draw the solution back into the syringe and re-inject it into the vial which contains the follitropin alfa powder. Once the powder has dissolved, draw it back into the syringe. Check again that there are no particles in it; do not use if the solution is not clear.
Up to 3 containers of powder may be dissolved in 1 ml of solvent.

- Replace the reconstitution needle with the **fine-bore needle** and expel the air bubbles. If you see air bubbles in the syringe, hold the syringe with the needle pointing upwards and gently flick the syringe with your finger until all the air collects at the top. Gently push the plunger until the air bubbles are gone.



- Immediately inject the solution: The doctor or nurse will have already advised you as to where to inject (e.g., abdomen, front of thigh). Wipe the chosen area with an alcohol swab. Firmly pinch the skin and insert the needle at a 45°-90° angle using a rapid motion. Inject under the skin, as you were instructed. Do not inject directly into a vein. Inject the solution by pushing gently on the plunger. Take as much time as you need to inject all the solution. When finished, withdraw the needle and clean the skin with an alcohol swab, using a circular motion.



- Dispose of all used items: Once you have finished your injection, immediately discard all needles and empty glass vials into the designated sharps container. Any unused solution must be discarded.

If you accidentally took a higher dosage, or if a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room, and bring the package of the medicine with you.
The effects of an overdose of Luveris 75 IU are not known; nevertheless, there is a possibility that ovarian hyperstimulation syndrome may occur (see section 4). However, this will only occur if hCG is administered (see section 2 under "Special warnings regarding use of the medicine").

If you forgot to use the medicine
Do not use a double dose to make up for the forgotten dose. Contact your doctor.
Adhere to the treatment regimen as recommended by the doctor.

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

4. SIDE EFFECTS

As with any medicine, use of Luveris 75 IU 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
Refer to a doctor immediately if you notice any of the side effects listed below. The doctor may ask you to stop using Luveris 75 IU.
Allergic reaction
Allergic reactions such as: rash, reddening of the skin, hives, swelling of the face with difficulty breathing can sometimes be serious. This side effect is very rare (may occur in less than one in 10,000 users)
Ovarian hyperstimulation syndrome
- Lower abdominal pain together with nausea or vomiting may be symptoms of ovarian hyperstimulation syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large sacs of fluid or cysts developed (see section 2 under "Ovarian hyperstimulation syndrome (OHSS)"). This side effect is common (may occur in 1-10 in 100 users). If this effect occurs, the doctor will have to examine you as soon as possible
- Serious blood clotting complications (thromboembolic events), mostly with severe OHSS; this side effect is very rare. This could cause chest pain, shortness of breath, stroke or heart attack (see section 2 under "Blood clotting problems")

Other common side effects
- Headache
- Nausea, vomiting, diarrhoea, abdominal discomfort or abdominal pain
- Sacs of fluid within the ovaries (ovarian cysts), breast pain and pelvic pain
- Local reactions at the injection site, such as: pain, itching, bruises, swelling or irritation

Torsion of the ovary and bleeding into the abdomen have not been reported with use of Luveris 75 IU; however, there have been rare cases reported following treatment with human menopausal gonadotropin (hMG), a urine-derived medicine also containing LH. Ectopic pregnancy may occur especially in women with a history of prior tubal diseases.

If a side effect has occurred, 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:
http://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE

- 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 package. The expiry date refers to the last day of that month.
- Do not store at a temperature above 25°C.
- Store the medicine in the original package in order to protect from light.
- Do not use Luveris 75 IU if you notice any signs of deterioration, such as discolouration of the powder or damage to the container.
- The medicine should be administered immediately after dissolving the powder.
- Do not use the solution if it contains particles or is not clear.
- Do not discard medicines via wastewater or household waste. Ask the pharmacist how to discard medicines that are not in use. These measures will help to protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Sucrose, disodium phosphate dihydrate, methionine, sodium dihydrogen phosphate monohydrate, polysorbate 20, phosphoric acid, concentrated (for pH adjustment), sodium hydroxide (for pH adjustment), nitrogen
Solvent: Water for injection

What the medicine looks like and the contents of the package
- Luveris 75 IU is supplied as a powder and solvent for solution for injection
- Each vial of powder contains 75 IU of lutropin alfa and each vial of solvent contains 1 ml of water for injection
- The package contains 1, 3 or 10 powder vials, with the same number of solvent vials
- Not all package sizes may be marketed

Registration Holder and Importer: Merck Serono Ltd., 18 Hakishon St., Yavne 81220
Manufacturer: Merck Serono S.A., Aubonne, Switzerland
Registration number of the medicine in the National Drug Registry of the Ministry of Health: 124 27 30373 00
Revised in November 2016 according to MOH guidelines.