## Luveris 75 IU

**NAME OF THE MEDICINAL PRODUCT**

Luveris® 75 IU, powder and solvent for solution for injection.

**QUALITATIVE AND QUANTITATIVE COMPOSITION**

One vial contains 75 IU of lutropin alfa (recombinant human luteinising hormone {LH}). Lutropin alfa is produced in genetically engineered Chinese hamster ovary (CHO) cells.

**PHARMACEUTICAL FORM**

Powder and solvent for solution for injection. Appearance of the product: white lyophilized pellet Appearance of the solvent: clear colourless solution

**CLINICAL PARTICULARS**

**Therapeutic indications**

Luveris® in association with a follicle stimulating hormone (FSH) preparation is Indicated for the stimulation of follicular development in women with severe LH and FSH deficiency. (*See clinical efficacy section)*

**Posology and method of administration**

Treatment with Luveris® should be initiated under the supervision of a physician experienced in the treatment of fertility disorders.

Self-administration of Luveris® should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

In LH and FSH deficient women, the objective of Luveris® therapy in association with FSH is to promote follicular development followed by final maturation after the administration of human chorionic gonadotrophin (hCG). Luveris® should be given as a course of daily injections simultaneously with FSH. If the patients is amenorrhoeic and haslow endogenous oestrogen secretion, treatment can commence at any time.

All clinical experience to date with Luveris® in this indication has been gained with concomitant administration of follitropin alfa.

Luveris® is intended for subcutaneous administration. The injection site should be alternated daily. The powder should be reconstituted, immediately prior to use, with the solvent provided.

A recommended regimen commences at 75 IU of lutropin alfa (ie. one vial of Luveris®) daily with 75-150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring (i) follicle size by ultrasound and (ii) oestrogen response

In clinical trials, Luveris has been shown to increase ovarian sensitivity to follitropin alfa. If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7 to 14 day intervals and preferably by 37.5 IU to 75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.

When an optimal response is obtained, a single injection of 5,000 IU to 10,000 IU hCG should be administered 24 to 48 hours after the last Luveris® and FSH injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration.

Alternatively, intrauterine insemination (IUI) or another medically assisted reproduction procedure may be performed based on the physician's judgement of the clinical case.

Luteal phase support may be considered since lack of substances with luteotrophic activity (LH/hCG) after ovulation may lead to premature failure of the corpus luteum.

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle.

**Contraindications**

Luveris® is contraindicated in patients with:

- hypersensitivity to gonadotrophins or to any of the excipients.
- ovarian, uterine, or mammary carcinoma;
- active, untreated tumours of the hypothalamus and pituitary gland;
- ovarian enlargement or cyst not due to polycystic ovarian disease;
- gynaecological haemorrhages of unknown origin

Luveris must not be used when a condition exists which would make a normal pregnancy impossible, such as:

- primary ovarian failure
- malformations of sexual organs incompatible with pregnancy
- fibroid tumours of the uterus incompatible with pregnancy

**Special warnings and special precautions for use**

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated.

In addition, patients should be evaluated for hypothyroidism, adrenocortical deficiency and hyperprolactinemia and appropriate specific treatment given.

In patients with porphyria or a family history of porphyria, gonadotrophins may increase the risk of an acute attack. Deterioration or a first appearance of this condition may require cessation of treatment.

*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.

Mild manifestations of OHSS may include abdominal pain, abdominal discomfort and distension, or enlarged ovaries. Moderate OHSS may additionally present with nausea, vomiting, ultrasound evidence of ascites or marked ovarian enlargement.

Severe OHSS further includes symptoms such as severe ovarian enlargement, weight gain, dyspnoea or oliguria. Clinical evaluation may reveal signs such as hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, pleural effusions, 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 oestradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in ART cycles.

In anovulation the risk of OHSS is increased by a serum oestradiol level > 900 pg/ml (3300 pmol/l) and by the presence of more than 3 follicles of 14 mm or more in diameter.

Adherence to recommended Luveris® and FSH dosage and regimen of administration can minimise the risk of ovarian hyperstimulation. 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 use barrier contraceptive methods for at least 4 days. As OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event, patients should be followed for at least two weeks after hCG administration.

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.

*Ovarian torsion*

Ovarian torsion has been reported after treatment with other gonadotropins. This may be associated with other risk factors such as OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, previous or current ovarian cyst and polycystic ovarian syndrome. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion.

*Multiple pregnancies*

In patients undergoing induction of ovulation, the incidence of multiple pregnancy is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancies, especially high order, carry an increased risk of adverse maternal and perinatal outcomes.

To minimise the risk of higher order multiple pregnancy, careful monitoring of ovarian response is recommended.

In patients undergoing Assisted Reproductive Technology (ART) procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient age.

*Pregnancy loss*

The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction 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.

*Congenital anomalies*

The prevalence of congenital anomalies after the use of ART may be slightly higher than after spontaneous conceptions. This could be due to parental factors (e.g. maternal age, genetics), ART procedures 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, thrombophilia or severe obesity (body mass index >30 kg/$m^2$), 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.

*Reproductive system neoplasms*

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women.

No direct comparison of Luveris®/FSH versus human menopausal gonadotrophin (hMG) has been performed. Comparison with historical data suggests that the ovulation rate obtained with Luveris®/FSH is similar to what can be obtained with hMG.

**Interaction with other medicinal products and other forms of interaction**

Luveris® should not be administered as a mixture with other medicinal products, in the same injection, except follitropin alfa for which studies have shown that co-administration does not significantly alter the activity, stability, pharmacokinetic nor pharmacodynamic properties of the active substances.

**Pregnancy and lactation**

Luveris® should not be administered during pregnancy or lactation

**Effects on ability to drive and use machines**

Luveris® does not interfere with the patient's ability to drive or use machines.

**Undesirable effects**

**a) General description**

Lutropin alfa is used for the stimulation of follicular development in association with follitropin alfa. In this context, it is difficult to attribute undesirable effects to any one of the substances used.

There is considerable post-marketing safety experience with human luteinising hormone (hLH)- containing medicinal products of urinary origin. The safety profile of Luveris® is expected to be very similar to that of urine derived hLH, with the exception of hypersensitivity reactions and application site disorders.

In a clinical trial, mild and moderate injection site reactions (bruising, pain, redness, itching or swelling) were reported in 7.4% and 0.9% of the injections, respectively. No severe injection site reactions were reported.

Ovarian hyperstimulation syndrome was observed in less than 6% of patients treated with Luveris®. No severe ovarian hyperstimulation syndrome was reported (section 4.4 Special warnings and special precautions for use).

In rare instances, thromboembolisms, adnexal torsion (a complication of ovarian enlargement), and haemoperitoneum have been associated with human menopausal gonadotrophin therapy. Although these adverse events were not observed, there is the possibility that they may also occur with Luveris®.

Ectopic pregnancy may also occur, especially in women with a history of prior tubal disease.

**b) Undesirable effects**

The following definition 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)

Frequency not known (cannot be estimated from the available data)

The following undesirable effects may be observed after administration of Luveris®.

<u>Immune system disorders</u>

Very rare: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Nervous system disorders

Common: Headache

Vascular disorders

Very rare: Thromboembolism, usually associated with severe OHSS

Gastrointestinal disorders

Common: Abdominal pain, abdominal discomfort, nausea, vomiting, diarrhoea

Reproductive system and breast disorders

Common: Mild or moderate OHSS (including associated symptomatology), ovarian cysts, breast pain, pelvic pain

General disorders and administration site conditions:

Common: Injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

**Overdose**

The effects of an overdose of lutropin alfa are unknown, nevertheless there is a possibility that ovarian hyperstimulation syndrome may occur, which is further described in 'Special warnings and special precautions for use'.

Single doses of up to 40,000 IU of lutropin alfa have been administered to healthy female volunteers without serious adverse events and were well tolerated.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic properties**

Pharmacotherapeutic group: gonadotrophins. ATC code: G03GA07

The primary effect resulting from administration of r-hLH is a dose-related increase of E2 secretion enhancing the effect of FSH administration on follicular growth.

**Pharmacokinetic properties**

Lutropin alfa pharmacokinetic characteristics are essentially similar to the pharmacokinetic characteristics of endogenous LH.

Absorption

Following subcutaneous administration of Luveris®, the absolute bioavailability is 56%.

The pharmacokinetics following single and repeated administration of lutropin alfa are comparable and the accumulation ratio of lutropin alfa is minimal (1.6-fold) [13].

Distribution

Following intravenous administration, lutropin alfa is rapidly distributed with an initial half-life of approximately 1 hour. The steady state volume of distribution (Vss) is in the range of 5 to 14 L [10,11,13].

Following intravenous administration, lutropin alfa shows linear pharmacokinetics, as assessed by AUC which is directly proportional to the dose administered.

Elimination

After subcutaneous administration of Luveris®, the apparent terminal half-life is in the range of 10 to 21 hours. Total body clearance is around1.8 L and less than 5% of the dose is excreted in the urine.

**Clinical efficacy**

In clinical trials, patients were defined by an endogenous serum LH level < 1.2 IU/L as measured in acentral laboratory. In these trials the ovulation rate per cycle was 70 to 75%. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

In one clinical study of women with hypogonadotropic hypogonadism and an endogenous serum LH concentration below 1.2 IU/L the appropriate dose of r-hLH was investigated. A dose of 75 IU r-hLHdaily (in combination with 150 IU r-hFSH) resulted in adequate follicular development and estrogen production. A dose of 25 IU r-hLH daily (in combination with 150 IU r-hFSH) resulted in insufficient follicular development.

**Preclinical safety data**

Extensive toxicology studies have been carried out with lutropin alfa in a range of animal models. These include the daily treatment of rats and monkeys with lutropin alfa for a duration of three months which resulted in well known pharmacological and morphological effects related to LH. No toxicity was observed in either species. As expected from the heterologous protein nature of the hormone, lutropin alfa raised an antibody response in experimental animals after a period that reduced the measurable serum LH levels but did not fully prevent its biological action. No signs of toxicity due to the development of antibodies to lutropin alfa were observed.

At doses of 10 IU/kg/day and greater, repeated administration of lutropin alfa to pregnant rats and rabbits caused impairment of reproductive function including resorption of foetuses and reduced body weight gain of the dams. However, drug-related teratogenesis was not observed in either animal model.

Other studies have shown that lutropin alfa is not mutagenic.

After intravenous administration of radiolabelled lutropin alfa to rats, tissue uptake paralleled the plasma profile of radioactivity with only a strong affinity to the ovaries in pregnant animals. Foetal

penetration of radioactivity was low. In lactating rats, radioactivity in milk was greater than or equal to that in plasma. Due to its heterologous protein nature, lutropin alfa produced moderate allergenic reactions in guinea pigs after intravenous challenge. For the same reason, a mild sensitisation was observed in guinea pigs after intradermal challenge.

**Incompatibilities**

This medicinal product must not be mixed with other medicinal products except follitropin alfa.

**Special precautions for storage**

Do not store above 30°C.

Keep out of the reach and sight of children.

Store in the original package in order to protect from light.

Do not use after the expiry date stated on the vials.

Do not use if you notice any visible signs of deterioration, such as discolouration of the powder or damage to the container.

**Pack Sizes**

The product is supplied in packs of 1, 3 or 10 vials with the corresponding number of solvent vials.

**Instructions for use and handling and disposal**

For immediate and single use following first opening and reconstitution.

The powder must be reconstituted with the solvent before use by gentle swirling.

The reconstituted solution should not be administered if it contains particles or is not clear.

Luveris® may be mixed with follitropin alfa and co-administered as a single injection.

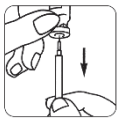
In this case Luveris® should be reconstituted first and then used to reconstitute the follitropin alfa powder.

In order to avoid the injection of large volumes, one vial of Luveris® can be reconstituted together with one or two ampoule(s)/vial(s) of follitropin alfa, 37.5 IU, 75 IU or 150 IU, in 1 ml of solvent.

Any unused product or waste material should be disposed of in accordance with local requirements.

**If you administer Luveris® to yourself, please carefully read the following instructions:**

- Wash your hands. It is important that your hands and the items you use be as clean as possible.
- Assemble everything you need. Find a clean area and lay out everything: one vial of Luveris®, one vial of solvent, two alcohol swabs, one syringe, one reconstitution needle for dissolving the powder in the solvent, a fine-bore needle for subcutaneous injection, a sharps container for safe 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. Then, 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® powder vial, pick up your syringe and slowly inject the solvent into the vial of Luveris®. Swirl gently without removing the syringe. Do not shake.

- After the powder has dissolved (which usually occurs immediately), check that the resulting solution is clear and does not contain any particles. Turn the vial upside down and gently draw the solution back into the syringe.
- You may also mix Luveris® and follitropin alfa as an alternative to injecting each product separately. After dissolving the Luveris® powder, draw the solution back into the syringe and re-inject it into the container with the follitropin alfa powder. Once the powder has dissolved, draw the solution back into the syringe. Inspect for particles as before, and do not use if the solution is not clear.
- Up to 3 containers of powder may be dissolved in 1 ml of solvent.
- Change the needle for the fine-bore needle and remove any 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. Gently push the plunger until the air bubbles are gone.

- Immediately inject the solution: Your doctor or nurse will have already advised you where to inject (e.g. tummy, front of thigh). Wipe the chosen area with an alcohol swab.
- Firmly pinch the skin together and insert the needle at a 45° to 90° angle using a dart-like motion. Inject under the skin, as you were taught.
- 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. Immediately 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 containers in the sharps container provided. Any unused solution must be discarded.

**Manufacturer**
Merck Serono SA
Succursale d'Aubonne
Zone industrielle de l'Ouriettaz
1170 Aubonne
Switzerland

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