Prescribing Information

Luveris® 75 IU

1. NAME OF THE MEDICINAL PRODUCT

Luveris® 75 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 75 IU of lutropin alfa*.

* recombinant human luteinising hormone (r-hLH) produced in genetically engineered Chinese hamster ovary (CHO) cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Appearance of the powder: white lyophilised pellet
Appearance of the solvent: clear colourless solution

The pH of the reconstituted solution is 7.5 to 8.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Luveris in association with a follicle stimulating hormone (FSH) preparation is recommended for the stimulation of follicular development in adult women with severe luteinising hormone (LH) and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/L.

4.2 Posology and method of administration

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

Posology

In LH and FSH deficient women, the objective of Luveris therapy in association with FSH is to develop a single mature Graafian follicle from which the oocyte will be liberated after the administration of

human chorionic gonadotropin (hCG). Luveris should be given as a course of daily injections simultaneously with FSH. Since these patients are amenorrhoeic and have low endogenous estrogen secretion, treatment can commence at any time.

Luveris should be administered concomitantly with follitropin alfa.

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

In clinical trials, Luveris has been shown to increase the 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 250 micrograms of r-hCG or 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) may be performed.

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 (see section 4.4).

Special populations

Elderly
There is no relevant use of Luveris in the elderly population. Safety and efficacy of Luveris in elderly patients have not been established.

Renal and hepatic impairment
Safety, efficacy and pharmacokinetics of Luveris in patients with renal or hepatic impairment have not been established.

Paediatric population
There is no relevant use of Luveris in the paediatric population.

Method of administration

Luveris is intended for subcutaneous use. The first injection of Luveris should be performed under direct medical supervision. The powder should be reconstituted immediately prior to use with the solvent provided. Self-administration of this medicinal product should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Luveris is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- tumours of the hypothalamus and pituitary gland
- ovarian enlargement or ovarian cyst unrelated to polycystic ovarian disease and of unknown origin
- gynaecological haemorrhages of unknown origin
- ovarian, uterine, or mammary carcinoma

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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.

Porphyria

In patients with porphyria or a family history of porphyria Luveris 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 estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

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 estradiol 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 pregnancy
In patients undergoing induction of ovulation, the incidence of multiple pregnancy and births is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancy, 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 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 or ART 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 malformations
The prevalence of congenital malformations after 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 carries 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 treatment regimens for infertility. It is not yet established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women.

Sodium content

Luveris contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no indication for the use of Luveris during pregnancy.
Data on a limited number of exposed pregnancies indicate no adverse reactions of gonadotropins on pregnancy, embryonal or foetal development, parturition or postnatal development following controlled ovarian stimulation. No teratogenic effect of Luveris has been observed in animal studies. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of Luveris.

Breast-feeding
Luveris is not indicated during breast-feeding.

Fertility
Luveris is indicated for the stimulation of follicular development, in association with FSH (see section 4.1).

4.7 Effects on ability to drive and use machines

Luveris has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Luveris is used for the stimulation of follicular development in association with follitropin alfa. In this

context, it is difficult to attribute adverse reactions to any one of the substances used.

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 (OHSS) was observed in less than 6% of patients treated with Luveris. No severe OHSS was reported (see section 4.4).

In rare instances, adnexal torsion (a complication of ovarian enlargement), and haemoperitoneum have been associated with human menopausal gonadotropin therapy. Although these adverse reactions 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.

List of adverse reactions
The following definitions 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 adverse reactions may be observed after administration of Luveris.

Immune system disorders
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 cyst, breast pain, pelvic pain

General disorders and administration site conditions:
Common: Injection site reaction (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

The effects of an overdose of Luveris are unknown. Nevertheless, there is a possibility that OHSS may occur (see section 4.4).

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

Management
Treatment is directed to symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, gonadotropins.
ATC code: G03GA07

Mechanism of action
Luteinising hormone (LH) and follicle stimulating hormone (FSH) are secreted from the anterior pituitary gland in response to gonadotropin-releasing hormone (GnRH) and play a complementary role in follicle development and ovulation. In theca cells, LH stimulates the secretion of androgens that are transferred to granulosa cells to be converted to estradiol (E2) by aromatase. In granulosa cells, FSH stimulates the development of ovarian follicles, while LH action is involved in follicle development, steroidogenesis and maturation.

Pharmacodynamic effects
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.

Clinical efficacy
In clinical trials, patients were defined by an endogenous serum LH level < 1.2 IU/L as measured in a central 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-hLH daily (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.

5.2 Pharmacokinetic properties

The pharmacokinetics of lutropin alfa have been studied in pituitary desensitised female volunteers from 75 IU up to 40,000 IU. The pharmacokinetic profile of lutropin alfa is similar to that of endogenous LH.

There is no pharmacokinetic interaction with follitropin alfa when administered simultaneously.

Distribution
Following intravenous administration, lutropin alfa is rapidly distributed with an initial half-life of approximately one hour and eliminated from the body with a terminal half-life of about 9 to 11 hours. The steady state volume of distribution is in the range of 5 to 14 L.

Lutropin alfa shows linear pharmacokinetics, as assessed by area under curve (AUC) which is directly proportional to the dose administered.

Following subcutaneous administration, the absolute bioavailability is 56% and the apparent terminal half-life is in the range of 8 to 21 hours. Dose proportionality after subcutaneous administration was demonstrated up to 450 IU. The lutropin alfa pharmacokinetics following single and repeated administration of Luveris are comparable and the accumulation ratio of lutropin alfa is minimal.

Elimination
Total body clearance is around 1.8 L/h and less than 5% of the dose is excreted in the urine.

5.3 Preclinical safety data

Non clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
Disodium phosphate dihydrate
Sodium dihydrogen phosphate monohydrate
Polysorbate 20
Phosphoric acid, concentrated (for pH adjustment)
Sodium hydroxide (for pH adjustment)
L- methionine
Nitrogen

Solvent
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

The powder is packaged in 3 mL neutral colourless glass (type I) vials. The vials are sealed with bromobutyl stoppers protected by aluminium seal rings and flip-off caps. The solvent is packaged either in 2 or 3 mL neutral colourless glass (type I) vials with a Teflon-coated rubber stopper.

Packs of 1, 3 or 10 vials with the corresponding number of solvent vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 vial(s) of follitropin alfa 75 IU in 1 mL of solvent.

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

7. REGISTRATION HOLDER

Merck Serono Ltd.
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8. MANUFACTURER:

Merck Serono S.A.
Succursale d'Aubonne,
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9. DATE OF REVISION OF THE TEXT

Revised in July 2022 according to MOH guidelines