ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 (powder 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 indicated for the stimulation of follicular development in adult women with severe luteinising hormone (LH) and FSH deficiency.

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 promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). Luveris should be given as a course of daily injections simultaneously with FSH. If the patient is amenorrhoeic and has 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 or another medically assisted reproduction procedure may be performed based on the physician's judgment 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 (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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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

3 years.

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 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. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/155/004
EU/1/00/155/005
EU/1/00/155/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 November 2000
Date of latest renewal: 24 January 2006

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance
Merck Serono S.A.
Succursale d'Aubonne
Zone Industrielle de l'Ouriettaz
1170 Aubonne
Switzerland

Name and address of the manufacturer responsible for batch release
Merck Serono S.p.A.
Via delle Magnolie 15 (loc. frazione Zona industriale)
70026 Modugno (BA)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LUVERIS 75 IU, VIALS

1. NAME OF THE MEDICINAL PRODUCT

Luveris 75 IU powder and solvent for solution for injection
lutropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains lutropin alfa 75 IU.

3. LIST OF EXCIPIENTS

Other ingredients: polysorbate 20, sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, phosphoric acid concentrated, sodium hydroxide, L-methionine and nitrogen.

One vial of solvent contains 1 mL water for injections. (EU/1/00/155/004-006)

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection / 1 vial of solvent
3 vials of powder for solution for injection / 3 vials of solvent
10 vials of powder for solution for injection / 10 vials of solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/155/004 (1 vial/ 1 vial)
EU/1/00/155/005 (3 vial/ 3 vials)
EU/1/00/155/006 (10 vials/ 10 vials)

13. BATCH NUMBER

Lot
Solvent Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

luveris 75 iu

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LUVERIS 75 IU, VIALS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Luveris 75 IU powder for injection
lutropin alfa
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

75 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LUVERIS 75 IU, SOLVENT VIALS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Luveris
water for injections
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user
Solvent in vials

Luveris 75 IU powder and solvent for solution for injection
lutropin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Luveris is and what it is used for

What Luveris is
Luveris is a medicine containing lutropin alfa, a recombinant Luteinising Hormone (LH) which is essentially similar to the hormone found naturally in humans, but is made by means of biotechnology. It belongs to the family of hormones called gonadotropins, which are involved in the normal control of reproduction.

What Luveris is used for
Luveris is recommended for the treatment of adult women who have been shown to produce very low levels of some of the hormones involved in the natural reproductive cycle. The medicine is used together with another hormone called Follicle Stimulating Hormone, (FSH), to bring about the development of follicles which are in the ovary, the structures maturing the eggs (ova). It is followed by treatment with a single dose of human Chorionic Gonadotropin (hCG), which leads to the release of an egg from the follicle (ovulation).

2. What you need to know before you use Luveris

Do not use Luveris
- if you are allergic to gonadotropins (such as luteinising hormone, follicle stimulating hormone or human chorionic gonadotropin), or any of the other ingredients of this medicine (listed in section 6).
- if you have cancer of ovaries, uterus or breast.
- if you have had a brain tumour diagnosed.
- if you have ovarian enlargement or sacs of fluid within the ovaries (ovarian cyst) of unknown origin.
- if you have unexplained vaginal bleeding.

Do not use Luveris if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before using this medicine.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Luveris.
You and your partner's fertility should be evaluated before the treatment is started.

It is recommended not to use Luveris if you have any condition that usually makes a normal pregnancy impossible, such as ovaries that do not work because of a condition called primary ovarian failure, or malformations of sexual organs.

Porphyria
Tell your doctor before you start treatment, if you or any member of your family have porphyria (an inability to break down porphyrins that may be passed on from parents to children).

Ovarian hyperstimulation syndrome (OHSS)
This medicine stimulates your ovaries. This increases your risk of developing ovarian hyperstimulation syndrome or OHSS. This is when your follicles develop too much and become large cysts. If you get lower abdominal pain, gain any weight rapidly, feel sick or are vomiting or if you have difficulty in breathing, talk to your doctor straight away who might ask 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 less likely. Luveris treatment seldom causes severe OHSS. This becomes more likely if the medicine that is used for final follicular maturation (containing human Chorionic Gonadotropin, hCG) is administered (see section 3 under "How much to use" for details). If you are developing OHSS your doctor may not give you any hCG in this treatment cycle and you may be told not to have sex or to use a barrier contraceptive method for at least four days.

Your doctor will ensure careful monitoring of ovarian response, based on ultrasound and blood sampling before and during the course of treatment.

Multiple pregnancy
When using Luveris, you have a higher risk of being pregnant with more than one child at the same time ("multiple pregnancy", mostly twins), than if you conceived 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 at the right times. When undergoing 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 undergoing assisted reproductive technologies or stimulation of your ovaries to produce eggs, you are more likely to have a miscarriage than the average woman.

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

Blood clotting problems (thromboembolic events)
Talk to your doctor before using Luveris 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 existing clots might become worse with Luveris treatment.

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

Children and adolescents
Luveris is not for use in children and adolescents below 18 years of age.

Other medicines and Luveris
Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Do not use Luveris as a mixture with other medicines in the same injection, except for follitropin alfa, if prescribed by your doctor.

Pregnancy and breast-feeding
Do not use Luveris if you are pregnant or breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

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

Luveris contains sodium
Luveris contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free".

3. How to use Luveris

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

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

How much to use
Luveris is usually used every day for up to three 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,** your doctor may increase your dose of FSH by preferably 37.5 to 75 IU at 7- to 14-day intervals.

Your physician may decide to extend your treatment up to 5 weeks.

When the desired response has been obtained, a single injection of hCG is given 24 to 48 hours after the last injections of Luveris and FSH. You are recommended to have sexual intercourse on the day of, and the day following, administration of the hCG. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on your doctor's judgment.

If an excessive response is obtained, treatment should be stopped and hCG withheld (see section 4 under "Ovarian hyperstimulation syndrome (OHSS)"). For the following cycle, your doctor will prescribe FSH at a lower dose than that of the previous cycle.

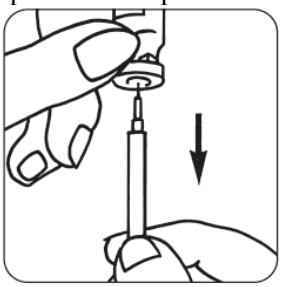
Method of administration
Luveris is intended for subcutaneous use which means it is given by injection under the skin. Each vial is for single use only.

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.

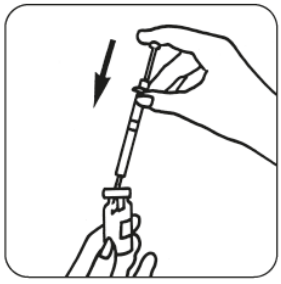
- Assemble everything you need. Find a clean area and lay out everything:
  - one vial of Luveris,
  - one vial of solvent,
  - two alcohol swabs,
  - one syringe,
  - one reconstitution needle for dissolving the powder in the solvent,
  - a fine-bore needle for subcutaneous injection,
  - a sharps container 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.

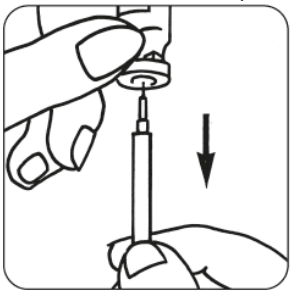


Carefully set the syringe down on the work-surface, taking care not to touch the needle.

- 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.**



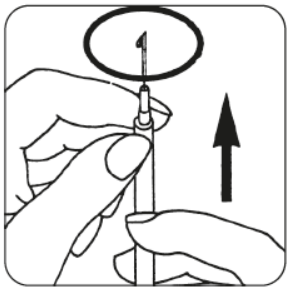
- After the powder has dissolved (which usually occurs immediately), check that the resulting solution is clear and does not contain any particles. Turn the vial upside down and gently draw the solution back into the syringe.



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.

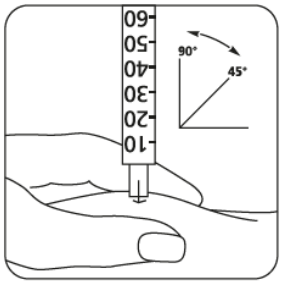
Up to 3 containers of powder may be dissolved in 1 mL of solvent.

- 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.

If you use more Luveris than you should
The effects of an overdose of Luveris are unknown, 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 “Warnings and precautions”).

If you forget to use Luveris
Do not use a double dose to make up for a forgotten dose. Please contact your doctor.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Contact your doctor straight away if you notice any of the below listed side effects. The doctor might ask you to stop using Luveris.

Allergic reaction
Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing can sometimes be serious. This side effect is very rare (may affect up to 1 in 10 000 people).

Ovarian hyperstimulation syndrome (OHSS)

- Lower abdominal pain together with nausea or vomiting may be the symptoms of ovarian hyperstimulation syndrome (OHSS). Your ovaries may have over-reacted to the treatment and formed large sacs of fluid or cysts (see section 2 under "Ovarian hyperstimulation syndrome (OHSS)"). This side effect is common (may affect up to 1 in 10 people). If this happens, your doctor will need to examine you as soon as possible.
- Serious blood clotting complications (thromboembolic events) usually with severe OHSS are found very rarely. This could cause chest pain, breathlessness, stroke or heart attack (see section 2 under "Blood clotting problems").

Other common side effects

- Headache
- Feeling sick, 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, bruising, swelling or irritation

Torsion of the ovary and bleeding into the abdomen have not been reported with Luveris, however, there have been rare cases reported following treatment with human menopausal gonadotropin (hMG), a urine-derived medication also containing LH.

Ectopic pregnancy (embryo implanted outside the womb) may occur especially in women with a history of prior tubal disease.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Luveris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton and the vials after EXP. The expiry date refers to the last day of that month.

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

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

The medicine should be administered immediately after dissolving the powder.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Luveris contains

- The active substance is lutropin alfa. One vial of powder for injection contains 75 IU (International Units).
- Lutropin alfa is recombinant human Luteinising Hormone (r-hLH), produced by recombinant DNA technology.
- The other ingredients of the powder are polysorbate 20, sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, concentrated phosphoric acid, sodium hydroxide, L-methionine and nitrogen.
- The solvent is water for injections.

What Luveris looks like and contents of the pack

- Luveris comes 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 injections.
- Luveris is supplied in packs containing 1, 3 or 10 vials of powder, together with the same number of solvent vials.

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Manufacturer
Merck Serono S.p.A.
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.