ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pergoveris 150 IU/75 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 IU (equivalent to 11 micrograms) of follitropin alfa* (r-hFSH) and 75 IU (equivalent to 3 micrograms) of lutropin alfa* (r-hLH).

After reconstitution, each ml of the solution contains 150 IU r-hFSH and 75 IU r-hLH per milliliter.

* produced in genetically engineered Chinese hamster Ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: white to off-white lyophilised pellet.
Solvent: clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pergoveris is indicated for the stimulation of follicular development in adult women with severe 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 Pergoveris should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

Posology

In LH and FSH deficient women (hypogonadotrophic hypogonadism), the objective of Pergoveris therapy is to develop a single mature Graafian follicle from which the oocyte will be liberated after the administration of human chorionic gonadotrophin (hCG). Pergoveris should be given as a course of daily injections. Since these patients are amenorrhoeic and have low endogenous oestrogen secretion, treatment can commence at any time.

Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response. A recommended regimen commences with one vial of Pergoveris daily. If less than one vial of Pergoveris daily is used, the follicular response may be unsatisfactory because the amount of lutropin alfa may be insufficient (see section 5.1).

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7-14 day intervals and preferably by 37.5-75 IU increments using a licensed follitropin alfa preparation. 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 24-48 hours after the last Pergoveris injection. 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.

Special populations

Older people
There is no relevant indication for the use of Pergoveris in the elderly population. Safety and effectiveness of Pergoveris in elderly patients have not been established.

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

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

Method of administration

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

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

4.3 Contraindications

Pergoveris is contraindicated in patients with:
- hypersensitivity to the active substances 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

Pergoveris must not be used when an effective response cannot be obtained, 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

Pergoveris contains potent gonadotrophic substances capable of causing mild to severe adverse reactions, and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonadotrophin therapy requires a certain time commitment by physicians and supportive health care professionals, as well as the availability of appropriate monitoring facilities. In women, safe and effective use of Pergoveris calls for monitoring of ovarian response with ultrasound, alone or preferably in combination with measurement of serum oestradiol levels, on a regular basis. There may be a degree of interpatient variability in response to FSH/LH administration, with a poor response to FSH/LH in some patients. The lowest effective dose in relation to the treatment objective should be used in women.

Porphyria

Patients with porphyria or a family history of porphyria should be closely monitored during treatment with Pergoveris. In these patients, Pergoveris may increase the risk of an acute attack. Deterioration or a first appearance of this condition may require cessation of treatment.

Treatment in women

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and appropriate specific treatment should be given.

Patients undergoing stimulation of follicular growth are at an increased risk of developing hyperstimulation in view of possible excessive oestrogen response and multiple follicular development.

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.

The following symptomatology may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea.

Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, or acute pulmonary distress, and thromboembolic events.

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 gonadotrophins, high absolute or rapidly rising serum oestradiol level (> 900 pg/ml or > 3,300 pmol/l in anovulation), previous episodes of OHSS and large number of developing ovarian follicles (3 follicles of ≥ 14 mm in diameter in anovulation).

Adherence to recommended Pergoveris 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 OHSS occur such as serum oestradiol level > 5,500 pg/ml or > 20,200 pmol/l and/or ≥ 40 follicles in total, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or to use barrier contraceptive methods for at least 4 days. OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event. It most often occurs after hormonal treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. Therefore patients should be followed for at least two weeks after hCG administration.
If severe OHSS occurs, gonadotropin treatment should be stopped if still ongoing. The patient should be hospitalised and specific therapy for OHSS started.This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

When a risk of OHSS is assumed, treatment discontinuation should be considered.

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 pregnancies 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 multiple pregnancy, careful monitoring of ovarian response is recommended.

The patients should be advised of the potential risk of multiple births before starting treatment. When risk of multiple pregnancies is assumed, treatment discontinuation should be considered.

Pregnancy loss

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

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.

Reproductive system neoplasms

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

Congenital malformation

The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) 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 gonadotrophins may further increase the risk. In these women, the benefits of gonadotrophin 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.

Sodium

Pergoveris contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Pergoveris 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 Pergoveris during pregnancy. Data on a limited number of exposed pregnancies indicate no adverse reactions of follitropin alfa and lutropin alfa on pregnancy, embryonal or foetal development, parturition or postnatal development following controlled ovarian stimulation. No teratogenic effect of such gonadotropins has been reported in animal studies. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of Pergoveris.

Breast-feeding

Pergoveris is not indicated during breast-feeding.

Fertility

Pergoveris is indicated for use in infertility (see section 4.1).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are headache, ovarian cysts and local injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection).
Mild or moderate ovarian hyperstimulation syndrome (OHSS) has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

Thromboembolism may occur very rarely, usually associated with severe OHSS (see section 4.4).

List of adverse reactions

Adverse reactions are listed below by MedDRA system organ class and by frequency. The frequency categories used are: 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).

Immune system disorders

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

Nervous system disorders

Very common: Headache

Vascular disorders

Very rare: Thromboembolism, usually associated with severe OHSS

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

Gastrointestinal disorders

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

Reproductive system and breast disorders

Very common: Ovarian cysts

Common: Breast pain, pelvic pain, mild or moderate OHSS (including associated symptomatology)

Uncommon: Severe OHSS (including associated symptomatology) (see section 4.4)

Rare: Complication of severe OHSS

General disorders and administration site conditions

Very common: Mild to severe injection site reactions (e.g. pain, erythema, haematoma, bruising, 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

Symptoms

The effects of an overdose of Pergoveris are unknown. Nevertheless there is a possibility that OHSS may occur, which is further described in section 4.4.

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: G03GA30.

Pergoveris is a preparation of follicle stimulating hormone and luteinising hormone produced by genetically engineered Chinese Hamster Ovary (CHO) cells.

Mechanism of action

In clinical trials the efficacy of the combination of follitropin alfa and lutropin alfa has been demonstrated in women with hypogonadotropic hypogonadism.

In the stimulation of follicular development in anovulatory women deficient in LH and FSH, the primary effect resulting from administration of lutropin alfa is an increase in oestradiol secretion by the follicles, the growth of which is stimulated by FSH.

Pharmacodynamic effects

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

Clinical efficacy

In one clinical study of women with hypogonadotrophic hypogonadism and an endogenous serum LH concentration below 1.2 IU/l the appropriate dose of r-hLH (lutropin alfa) was investigated. A dose of 75 IU r-hLH daily (in combination with 150 IU follitropin alfa (r-hFSH)) resulted in adequate follicular development and oestrogen production. A dose of 25 IU r-hLH daily (in combination with 150 IU follitropin alfa) resulted in insufficient follicular development. Therefore, administration of less than one vial of Pergoveris daily may provide too little LH-activity to ensure adequate follicular development.

5.2 Pharmacokinetic properties

Follitropin alfa and lutropin alfa have shown the same pharmacokinetic profile as follitropin alfa and lutropin alfa separately.

Follitropin alfa

Distribution
Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and eliminated from the body with a terminal half-life of about one day. The steady state volume of distribution is 10 l.
Following subcutaneous administration, the absolute bioavailability is about 70%. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3-4 days. In women whose endogenous gonadotrophin secretion is suppressed, follitropin alfa has nevertheless been shown to effectively stimulate follicular development and steroidogenesis, despite unmeasurable LH levels.

Elimination
Total clearance is 0.6 l/h and one-eighth of the follitropin alfa dose is excreted in the urine.

Lutropin alfa

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 10-12 hours. The steady state volume of distribution is around 10-14 l. Lutropin alfa shows linear pharmacokinetics, as assessed by AUC which is directly proportional to the dose administered. Following subcutaneous administration, the absolute bioavailability is approximately 60%; the terminal half-life is slightly prolonged. The lutropin alfa pharmacokinetics following single and repeated administration of lutropin alfa are comparable and the accumulation ratio of lutropin alfa is minimal. The mean residence time is approximately 5 hours.

Elimination
Total clearance is around 2 l/h, and less than 5% of the dose is excreted in the urine.

Pharmacokinetic/pharmacodynamic relationships
There is no pharmacokinetic interaction with follitropin alfa when administered simultaneously.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sucrose
Polysorbate 20
Methionine
Disodium phosphate dihydrate
Sodium dihydrogen phosphate monohydrate
Phosphoric acid, concentrated (for pH adjustment)
Sodium hydroxide (for pH adjustment)

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

Unopened vials

3 years.

Reconstituted solution

Pergoveris is for an immediate and single use following first opening and reconstitution therefore the product may not be stored once opened and reconstituted.

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

Powder: 3 ml vials (Type I glass) with a stopper (bromobutyl rubber) and aluminium flip-off cap.
1 vial contains 11 micrograms r-hFSH and 3 micrograms r-hLH.

Solvent: 3 ml vials (Type I glass) with a Teflon coated rubber stopper and aluminium flip-off cap.
1 vial of solvent contains 1 ml of water for injections.

Pack sizes of 1, 3 and 10 vials with the corresponding number of solvent's vial (1, 3 and 10 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.

Reconstitution

The pH of the reconstituted solution is 6.5-7.5.

Pergoveris 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.

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

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

7. MARKETING AUTHORISATION HOLDER

Merck Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/07/396/001
EU/1/07/396/002
EU/1/07/396/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 June 2007
Date of latest renewal: 22 May 2012

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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER 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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances

Merck Serono S.A.
Zone Industrielle de l'Ouriettaz
CH-1170 Aubonne
Switzerland

Or

Merck S.L.
C/ Batanes 1
Tres Cantos
E-28760 Madrid
Spain

Name and address of the manufacturer responsible for batch release

Merck Serono S.p.A.
Via delle Magnolie 15 (Zona Industriale)
I-70026 Modugno (Bari)
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**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 1, 3, 10 VIALS OF POWDER AND SOLVENT

1. NAME OF THE MEDICINAL PRODUCT

Pergoveris 150 IU/75 IU powder and solvent for solution for injection.
Follitropin alfa/lutropin alfa

2. STATEMENT OF THE ACTIVE SUBSTANCE(S)

One vial contains 150 IU (equivalent to 11 micrograms) of follitropin alfa (r-hFSH) and 75 IU (equivalent to 3 micrograms) of lutropin alfa (r-hLH).

3. LIST OF EXCIPIENTS

Other ingredients:
Powder: disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, methionine, polysorbate 20, sucrose.
Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection.

1 vial of powder (11 micrograms r-hFSH and 3 micrograms r-hLH).
1 vial of solvent (1 ml).
3 vials of powder.
3 vials of solvent.
10 vials of powder.
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.
Read the leaflet for the shelf life of the reconstituted medicine.

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/396/001	1 vial of powder for solution for injection. 1 vial of solvent.
EU/1/07/396/002	3 vials of powder for solution for injection. 3 vials of solvent.
EU/1/07/396/003	10 vials of powder for solution for injection. 10 vials of solvent.

13. BATCH NUMBER

Batch
Solvent Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pergoveris

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PERGOVERIS 150 IU/75 IU
VIAL LABEL

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

Pergoveris 150 IU/75 IU powder for solution for injection
Follitropin alfa/Lutropin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 IU r-hFSH/75 IU r-hLH

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL

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

Solvent for Pergoveris
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Pergoveris 150 IU/75 IU powder and solvent for solution for injection
Follitropin alfa/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, nurse or pharmacist.
- 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, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pergoveris is and what it is used for
2. What you need to know before you use Pergoveris
3. How to use Pergoveris
4. Possible side effects
5. How to store Pergoveris
6. Contents of the pack and other information

1. What Pergoveris is and what it is used for

What Pergoveris is

Pergoveris contains two different active substances called “follitropin alfa” and “lutropin alfa”. Both belong to the family of hormones called “gonadotropins”, which are involved in reproduction and fertility.

What Pergoveris is used for

This medicine is used to stimulate the development of follicles (each containing an egg) in your ovaries. This is to help you get pregnant. It is for use in adult women (18 years old or above) who have low levels (severe deficiency) of “follicle stimulating hormone” (FSH) and “luteinising hormone” (LH). These women are usually infertile.

How Pergoveris works

The active substances in Pergoveris are copies of the natural hormones FSH and LH. In your body:
- FSH stimulates the production of eggs
- LH stimulates the release of the eggs.

By replacing the missing hormones, Pergoveris allows women with low levels of FSH and LH to develop a follicle. This will then release an egg, after an injection of the hormone “human chorionic gonadotropin (hCG)”. This helps the women to become pregnant.

2. What you need to know before you use Pergoveris

You and your partner's fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility problems.

Do not use Pergoveris:

- if you are allergic to follicle stimulating hormone (FSH), luteinising hormone (LH) or any of the other ingredients of this medicine (listed in section 6)
- if you have a brain tumour (in your hypothalamus or pituitary gland)
- if you have large ovaries or sacs of fluid within your ovaries (ovarian cysts) of unknown origin
- if you have unexplained vaginal bleeding
- if you have cancer in your ovaries, womb or breasts
- if you have a condition that would make a normal pregnancy impossible, such as an early menopause, malformed sex organs or benign tumours of the womb.

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Pergoveris.

Porphyria

Talk to your doctor before you start your treatment.If you or any member of your family have porphyria (an inability to breakdown porphyrins that may be passed on from parents to children).
Tell your doctor straight away if:

- your skin becomes fragile and easily blistered, especially skin that has been frequently exposed to sunlight
- you have stomach, arm or leg pain.

In case of above events your doctor may recommend that you stop treatment.

Ovarian Hyper-Stimulation Syndrome (OHSS)

This medicine stimulates your ovaries. This increases your risk of developing Ovarian Hyper-Stimulation 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.They might ask you to stop using this medicine (see in section 4. under “Most serious side effects”).

In case you are not ovulating and if the recommended dose and schedule of administration are adhered to, the occurrence of severe OHSS is less likely. Pergoveris treatment seldom causes severe OHSS. This becomes more likely if the medicine that is used for final follicular maturation (containing human chorionic gonadotrophin , hCG) is administered (see in 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 that you should use a barrier contraceptive method for at least four days.
Your doctor will ensure, careful monitoring of the ovarian response, based on ultrasound and blood tests (oestradiol measurements) before and during the course of treatment.

Multiple pregnancy

When using Pergoveris, 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 Pergoveris at the right times.

To minimise the risk of multiple pregnancy, ultrasound scans as well as blood tests are recommended.

Miscarriage

When undergoing stimulation of your ovaries to produce eggs, you are more likely to have a miscarriage than the average woman.

Ectopic pregnancy

Women who have ever had blocked or damaged fallopian tubes (tubal disease) are at risk of pregnancy where the embryo is implanted outside the womb (ectopic pregnancy). This is whether the pregnancy is obtained by spontaneous conception or with fertility treatments.

Blood clotting problems (thromboembolic events)

Talk to your doctor before using Pergoveris 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 Pergoveris 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 regimens for infertility treatment.

Allergic reactions

There have been isolated reports of non-serious allergic reactions to Pergoveris. If you have ever had this type of reaction to a similar medicine, talk to your doctor before using Pergoveris.

Children and adolescents

Pergoveris is not for use in children and adolescents below 18 years old.

Other medicines and Pergoveris

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

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

Pregnancy and breast-feeding

Do not use Pergoveris if you are pregnant or breast-feeding.

Driving and using machines

It is not expected that this medicine will affect your ability to drive or use machines.

Information about the sodium content of Pergoveris

Pergoveris contains less than 1 mmol sodium (23 mg) per dose. It is essentially “sodium-free”.

3. How to use Pergoveris

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

Using this medicine

- Pergoveris is intended to be given by injection just under the skin (subcutaneously). To minimise skin irritation, select a different injection site each day.
- It comes as a powder and liquid, which you need to mix together and then use straight away.
- Your doctor or nurse will show you how to prepare and inject this medicine. They will supervise your first injection.
- If they are satisfied that you can administer Pergoveris safely, you can then prepare and inject the medicine yourself at home. When you do this, please carefully read and follow the instructions hereafter called "How to prepare and use the Pergoveris powder and solvent".

How much to use

The usual starting dose is one vial of Pergoveris every day.

- According to your response, your doctor may decide to add every day a dose of follitropin alfa to your Pergoveris injection. In this case, the follitropin alfa dose is usually increased every 7 or every 14 days by 37.5 to 75 IU.
- Treatment is continued until you get the desired response. This is when you have developed a suitable follicle, as assessed using ultrasound scans and blood tests.
- This may take up to 5 weeks.

When you get the desired response, you will be given a single injection of human chorionic gonadotropin (hCG) 24 to 48 hours after your last Pergoveris injection. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination (IUI) may be performed.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see in section 2. under "Ovarian Hyper-Stimulation Syndrome"). In this case, your doctor will give you a lower follitropin alfa dose in the following cycle.

How to prepare and use the Pergoveris powder and solvent

Before starting the preparation, please read these instructions the whole way through first:
Give yourself the injection at the same time each day.

1. Wash your hands and find a clean area

- It is important that your hands and the items you use be as clean as possible
- A good place is a clean table or kitchen surface

2. Get together everything you need and lay them out

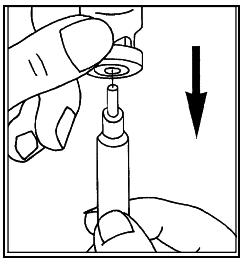
- 1 vial containing Pergoveris powder
- 1 vial containing water for injections (solvent)

Not provided in the pack:

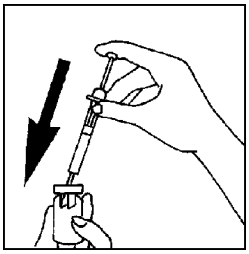
- 2 alcohol swabs
- 1 empty syringe for injection
- 1 needle for preparation
- 1 fine bore needle for injection under the skin

- one sharps container for safe disposal of glass and needles

3. Preparing the solution

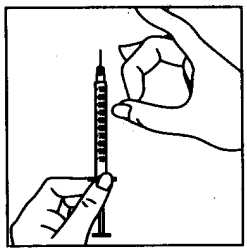


- Remove the protective cap from the vial filled with water (solvent vial).
- Attach the needle for preparation to the empty syringe for injection.
- Draw up some air into the syringe by pulling the plunger to approximately the 1 ml mark.
- Insert the needle into the vial, push the plunger to expel the air.
- Turn the vial upside down and gently draw up all the water (solvent).
- Remove the syringe from the vial and set it down carefully. Do not touch the needle and do not allow the needle to touch any surface.



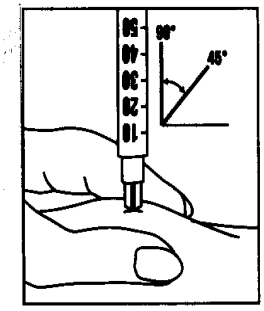
- Remove the protective cap from the vial filled with Pergoveris powder.
- Pick up your syringe and slowly inject the contents of the syringe into the vial of powder.
- Swirl gently without removing the syringe. Do not shake.
- After the powder has dissolved (which usually occurs immediately), check that the resulting solution is clear and does not contain any particles.
- Turn the vial upside down, gently draw the solution back into the syringe. Check for particles as before, and do not use if the solution is not clear.

4. Getting the syringe ready for injection



- Change the needle for the fine bore needle.
- 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. Push the plunger until the air bubbles are gone.

5. Injecting the dose



- Immediately inject the solution. Your doctor or nurse will have already advised you where to inject (e.g. tummy, front of thigh). To minimise skin irritation, select a different injection site each day.
- Clean the chosen skin area with an alcohol swab using a circular motion.
- 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.
- Then withdraw the needle and clean the skin with a new alcohol swab using a circular motion.

6. After the injection

Dispose of all used items. Once you have finished your injection, immediately discard all needles and empty vials in your sharps container. Any unused solution must be discarded.

If you use more Pergoveris than you should

The effects of an overdose of Pergoveris are unknown, nevertheless one could expect OHSS to occur. However this will only occur if hCG is administered (see in section 2. under "Ovarian Hyper-Stimulation Syndrome").

If you forget to use Pergoveris

Do not take a double dose to make up for a forgotten dose. Please contact your doctor.

If you have any further question 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 every body gets them.

Most 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 Pergoveris.

Allergic reactions

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.

Ovarian Hyper-Stimulation Syndrome

- Lower abdominal pain together with nausea or vomiting. These may be the symptoms of Ovarian Hyper-Stimulation Syndrome (OHSS). Your ovaries may have over-reacted to the treatment and formed large sacs of fluid or cysts (see also in section 2. under "Ovarian Hyper-Stimulation Syndrome") .This side effect is common. If this happens, your doctor will need to examine you as soon as possible.
- The OHSS may become severe with clearly enlarged ovaries, decreased urine production, weight gain, difficulty in breathing and/or possible fluid accumulation in your stomach or chest. This side effect is uncommon (may affect up to 1 in 100 people).
- Complications of OHSS such as twisting of ovaries or blood clotting occur rarely (may affect up to 1 in 1,000 people).
- Serious blood clotting problems (thromboembolic events) usually with severe OHSS are found very rarely. This could cause chest pain, breathlessness, stroke or heart attack. In rare cases this can also happen independently of OHSS (see also in section 2. under "Blood clotting problems).

Other side effects

Very common (may affect more than 1 in 10 people)

- sacs of fluid within the ovaries (ovarian cysts)
- headache

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

Common (may affect up to 1 in 10 people):

- diarrhoea
- breast pain
- feeling sick or vomiting
- abdominal or pelvic pain
- abdominal cramp or bloating.

Very rare (may affect up to 1 in 10,000 people):

- Your asthma may get worse.

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. 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 Pergoveris

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 vials and the carton 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.

The medicine must be administered immediately after reconstitution.

Do not use Pergoveris if you notice any visible signs of deterioration.

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

Do not throw 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 Pergoveris contains

The active substances are follitropin alfa and lutropin alfa.

- One vial contains 150 IU (equivalent to 11 micrograms) of follitropin alfa and 75 IU (equivalent to 3 micrograms) of lutropin alfa.
  After reconstitution, each ml of the solution contains 150 IU follitropin alfa and 75 IU lutropin alfa per milliliter.
- The other ingredients are
  Powder: sucrose, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, methionine, polysorbate 20, concentrated phosphoric acid and sodium hydroxide.
  Solvent: water for injections. Each vial contains 1 ml.

What Pergoveris looks like and contents of the pack

- Pergoveris is presented as a powder and solvent for solution for injection.
- The powder is a white to off-white lyophilised pellet in a glass vial.
- The solvent is a clear colourless liquid in a glass vial.
- Pergoveris is supplied in packs of 1, 3 and 10 vials of powder with the corresponding number of solvent's vials (1, 3 and 10 vials). Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicine Agency web site: http://www.ema.europa.eu.