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 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**

**Elderly**
There is no relevant indication for the use of Pergoveris in the elderly population. Safety and effectiveness of this medicinal product in elderly patients have not been established.

**Renal and hepatic impairment**
Safety, efficacy, and pharmacokinetics of this medicinal product in patients with renal or hepatic impairment have not been established.

**Paediatric population**
There is no relevant use of this medicinal product in the paediatric population.

**Method of administration**
Pergoveris is intended for subcutaneous administration. The first injection should be performed under direct medical supervision. The powder should be reconstituted immediately prior to use with the solvent provided. Self-administration 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 assisted reproductive technologies (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/m²), 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 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).

Tabulated 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), not known (cannot be estimated from the available data).

**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 recombinant human follicle stimulating hormone (follitropin alfa, r-hFSH) and recombinant human luteinising hormone (lutropin alfa, r-hLH) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

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 was investigated. A dose of 75 IU r-hLH daily (in combination with 150 IU r-hFSH) resulted in adequate follicular development and oestrogen production. A dose of 25 IU r-hLH daily (in combination with 150 IU r-hFSH) 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.

Clinical studies with Pergoveris were conducted with a freeze-dried formulation. A comparative clinical study between the freeze-dried and the liquid formulation showed bioequivalence between the two formulations.

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.
1. **NAME OF THE MEDICINAL PRODUCT**

Pergoveris (300 IU + 150 IU)/0.48 mL solution for injection in pre-filled pen

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each multidose pre-filled pen contains 300 IU (equivalent to 22 micrograms) of follitropin alfa* (r-hFSH) and 150 IU (equivalent to 6 micrograms) of lutropin alfa* (r-hLH) in 0.48 mL solution.

*recombinant human follitropin alfa and recombinant human lutropin alfa are produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection (injection).

Clear, colourless to slightly yellow solution.

The pH of the solution is 6.5 – 7.5, its osmolality is 250 – 400 mOsm/kg.

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 treatment regimen commences with the recommended dose of Pergoveris containing 150 IU r-hFSH/75 IU r-hLH daily. If less than the recommended dose 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**

**Elderly**
There is no relevant indication for the use of Pergoveris in the elderly population. Safety and effectiveness of this medicinal product in elderly patients have not been established.

**Renal and hepatic impairment**
Safety, efficacy, and pharmacokinetics of this medicinal product in patients with renal or hepatic impairment have not been established.

**Paediatric population**
There is no relevant use of this medicinal product in the paediatric population.

**Method of administration**

Pergoveris is intended for subcutaneous administration. The first injection should be performed under direct medical supervision. Self-administration should only be performed by patients who are well motivated, adequately trained and with access to expert advice.

For instructions on the use of this medicinal product, 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 $\geq 40$ 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 assisted reproductive technologies (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/m²), 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 solution for injection in pre-filled pen must not be administered as a mixture with other medicinal products in the same injection.

Pergoveris solution for injection in pre-filled pen may be administered concomitantly with a licensed follitropin alfa preparation as separate injections.

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 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).
Tabulated 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), not known (cannot be estimated from the available data).

**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 recombinant human follicle stimulating hormone (follitropin alfa, r-hFSH) and recombinant human luteinising hormone (lutropin alfa, r-hLH) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

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 was investigated. A dose of 75 IU r-hLH daily (in combination with 150 IU r-hFSH) resulted in adequate follicular development and oestrogen production. A dose of 25 IU r-hLH daily (in combination with 150 IU r-hFSH) resulted in insufficient follicular development. Therefore, administration of Pergoveris containing less than 75 IU r-hLH 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.

Clinical studies with Pergoveris were conducted with a freeze-dried formulation. A comparative clinical study between the freeze-dried and the liquid formulation showed bioequivalence between the two formulations.

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
Sucrose
Arginine monohydrochloride
Poloxamer 188
Methionine
Phenol
Disodium phosphate dihydrate
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide (for pH adjustment)
Phosphoric acid, concentrated (for pH adjustment)
Water for injections

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

Chemical and physical in-use stability has been demonstrated for 28 days at 25°C. Once opened, the product may be stored for a maximum of 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.
6.4 Special precautions for storage

Store in refrigerator (2°C- 8°C). Do not freeze.
Store in the original package in order to protect from light.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

Colourless 3 mL glass cartridge (type I borosilicate glass, with a grey bromobutyl rubber plunger stopper and a crimp cap made with grey rubber stopper septum and aluminium) pre-assembled in a pre-filled pen.

Each Pergoveris (300 IU + 150 IU)/0.48 mL pre-filled pen contains 0.48 mL of solution for injection and can deliver two doses of Pergoveris 150 IU/75 IU.

Pack of 1 Pergoveris (300 IU + 150 IU)/0.48 mL pre-filled pen and 5 injection needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Only clear solution without particles should be used.

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

For instructions on the use of this medicinal product, see the package leaflet, section 'Instructions for use'.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/07/396/004

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}
1. **NAME OF THE MEDICINAL PRODUCT**

Pergoveris (450 IU + 225 IU)/0.72 mL solution for injection in pre-filled pen

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each multidose pre-filled pen contains 450 IU (equivalent to 33 micrograms) of follitropin alfa* (r-hFSH) and 225 IU (equivalent to 9 micrograms) of lutropin alfa* (r-hLH) in 0.72 mL solution.

*recombinant human follitropin alfa and recombinant human lutropin alfa are produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection (injection).
Clear, colourless to slightly yellow solution.

The pH of the solution is 6.5 – 7.5, its osmolality is 250 – 400 mOsm/kg.

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 treatment regimen commences with the recommended dose of Pergoveris containing 150 IU r-hFSH/75 IU r-hLH daily. If less than the recommended dose 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**

**Elderly**
There is no relevant indication for the use of Pergoveris in the elderly population. Safety and effectiveness of this medicinal product in elderly patients have not been established.

**Renal and hepatic impairment**
Safety, efficacy, and pharmacokinetics of this medicinal product in patients with renal or hepatic impairment have not been established.

**Paediatric population**
There is no relevant use of this medicinal product in the paediatric population.

**Method of administration**

Pergoveris is intended for subcutaneous administration. The first injection should be performed under direct medical supervision. Self-administration should only be performed by patients who are well motivated, adequately trained and with access to expert advice.

For instructions on the use of this medicinal product, 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 assisted reproductive technologies (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/m²), 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 solution for injection in pre-filled pen must not be administered as a mixture with other medicinal products in the same injection.

Pergoveris solution for injection in pre-filled pen may be administered concomitantly with a licensed follitropin alfa preparation as separate injections.

**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 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).
Tabulated 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), not known (cannot be estimated from the available data).

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 recombinant human follicle stimulating hormone (follitropin alfa, r-hFSH) and recombinant human luteinising hormone (lutropin alfa, r-hLH) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

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 was investigated. A dose of 75 IU r-hLH daily (in combination with 150 IU r-hFSH) resulted in adequate follicular development and oestrogen production. A dose of 25 IU r-hLH daily (in combination with 150 IU r-hFSH) resulted in insufficient follicular development. Therefore, administration of Pergoveris containing less than 75 IU r-hLH 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.

Clinical studies with Pergoveris were conducted with a freeze-dried formulation. A comparative clinical study between the freeze-dried and the liquid formulation showed bioequivalence between the two formulations.

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

Sucrose
Arginine monohydrochloride
Poloxamer 188
Methionine
Phenol
Disodium phosphate dihydrate
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide (for pH adjustment)
Phosphoric acid, concentrated (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Chemical and physical in-use stability has been demonstrated for 28 days at 25°C. Once opened, the product may be stored for a maximum of 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.
6.4 Special precautions for storage

Store in refrigerator (2°C- 8°C). Do not freeze.
Store in the original package in order to protect from light.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

Colourless 3 mL glass cartridge (type I borosilicate glass, with a grey bromobutyl rubber plunger stopper and a crimp cap made with grey rubber stopper septum and aluminium) pre-assembled in a pre-filled pen.

Each Pergoveris (450 IU + 225 IU)/0.72 mL pre-filled pen contains 0.72 mL of solution for injection and can deliver three doses of Pergoveris 150 IU/75 IU.

Pack of 1 Pergoveris (450 IU + 225 IU)/0.72 mL pre-filled pen and 7 injection needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Only clear solution without particles should be used.

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

For instructions on the use of this medicinal product, see the package leaflet, section 'Instructions for use'.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/07/396/005

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}
1. NAME OF THE MEDICINAL PRODUCT

Pergoveris (900 IU + 450 IU)/1.44 mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each multidose pre-filled pen contains 900 IU (equivalent to 66 micrograms) of follitropin alfa* (r-hFSH) and 450 IU (equivalent to 18 micrograms) of lutropin alfa* (r-hLH) in 1.44 mL solution.

*recombinant human follitropin alfa and recombinant human lutropin alfa are produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear, colourless to slightly yellow solution.

The pH of the solution is 6.5 – 7.5, its osmolality is 250 – 400 mOsm/kg.

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 treatment regimen commences with the recommended dose of Pergoveris containing 150 IU r-hFSH/75 IU r-hLH daily. If less than the recommended dose 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**

**Elderly**
There is no relevant indication for the use of Pergoveris in the elderly population. Safety and effectiveness of this medicinal product in elderly patients have not been established.

**Renal and hepatic impairment**
Safety, efficacy, and pharmacokinetics of this medicinal product in patients with renal or hepatic impairment have not been established.

**Paediatric population**
There is no relevant use of this medicinal product in the paediatric population.

**Method of administration**

Pergoveris is intended for subcutaneous administration. The first injection should be performed under direct medical supervision. Self-administration should only be performed by patients who are well motivated, adequately trained and with access to expert advice.

For instructions on the use of this medicinal product, 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 assisted reproductive technologies (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/m²), 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 solution for injection in pre-filled pen must not be administered as a mixture with other medicinal products in the same injection.

Pergoveris solution for injection in pre-filled pen may be administered concomitantly with a licensed follitropin alfa preparation as separate injections.

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 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).
Tabulated 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), not known (cannot be estimated from the available data).

**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 recombinant human follicle stimulating hormone (follitropin alfa, r-hFSH) and recombinant human luteinising hormone (lutropin alfa, r-hLH) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

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

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 was investigated. A dose of 75 IU r-hLH daily (in combination with 150 IU r-hFSH) resulted in adequate follicular development and oestrogen production. A dose of 25 IU r-hLH daily (in combination with 150 IU r-hFSH) resulted in insufficient follicular development.

Therefore, administration of Pergoveris containing less than 75 IU r-hLH 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.

Clinical studies with Pergoveris were conducted with a freeze-dried formulation. A comparative clinical study between the freeze-dried and the liquid formulation showed bioequivalence between the two formulations.

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
Sucrose
Arginine monohydrochloride
Poloxamer 188
Methionine
Phenol
Disodium phosphate dihydrate
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide (for pH adjustment)
Phosphoric acid, concentrated (for pH adjustment)
Water for injections

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

Chemical and physical in-use stability has been demonstrated for 28 days at 25°C. Once opened, the product may be stored for a maximum of 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.
6.4 Special precautions for storage

Store in refrigerator (2°C- 8°C). Do not freeze.
Store in the original package in order to protect from light.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

Colourless 3 mL glass cartridge (type I borosilicate glass, with a grey bromobutyl rubber plunger stopper and a crimp cap made with grey rubber stopper septum and aluminium) pre-assembled in a pre-filled pen.

Each Pergoveris (900 IU + 450 IU)/1.44 mL pre-filled pen contains 1.44 mL of solution for injection and can deliver six doses of Pergoveris 150 IU/75 IU.

Pack of 1 Pergoveris (900 IU + 450 IU)/1.44 mL pre-filled pen and 14 injection needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Only clear solution without particles should be used.

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

For instructions on the use of this medicinal product, see the package leaflet, section 'Instructions for use'.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/07/396/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZAION

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

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
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

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 requirements for submission of periodic safety update reports 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 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

OUTER CARTON

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, sodium hydroxide (for pH adjustment) and concentrated phosphoric acid (for pH adjustment).
Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection.

1 vial of powder.
1 vial of solvent.
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 AUTHORITY

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

12. MARKETING AUTHORIZATION 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

15. INSTRUCTIONS ON USE
16. INFORMATION IN BRAILLE

pergoveris 150 iu/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

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
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PERGOVERIS (300 IU + 150 IU)/0.48 ML SOLUTION FOR INJECTION IN PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Pergoveris (300 IU + 150 IU)/0.48 mL solution for injection in pre-filled pen
Follitropin alfa/Lutropin alfa

2. STATEMENT OF THE ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 300 IU (equivalent to 22 micrograms) of follitropin alfa (r-hFSH) and 150 IU (equivalent to 6 micrograms) of lutropin alfa (r-hLH) in 0.48 mL.

3. LIST OF EXCIPIENTS

Excipients: sucrose, arginine monohydrochloride, poloxamer 188, methionine, phenol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide and concentrated phosphoric acid (for pH adjustment), and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 multidose pre-filled pen of 0.48 mL solution
5 injection needles

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
Once opened, the medicinal product may be stored for a maximum of 28 days at 25°C.
9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. 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 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 AUTHORIZATION NUMBER(S)

EU/1/07/396/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pergoveris (300 iu + 150 iu)/0.48 ml pen

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

**PERGOVERIS (300 IU + 150 IU)/0.48 ML SOLUTION FOR INJECTION IN PRE-FILLED PEN, PEN LABEL**

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

Pergoveris (300 IU + 150 IU)/0.48 mL injection
Follitropin alfa/Lutropin alfa
Subcutaneous use

### 2. METHOD OF ADMINISTRATION

### 3. EXPIRY DATE

EXP
Shelf life after first use: 28 days

### 4. BATCH NUMBER

Batch

### 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 IU r-hFSH-150 IU r-hLH/0.48 mL

### 6. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PERGOVERIS (450 IU + 225 IU)/0.72 ML SOLUTION FOR INJECTION IN PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Pergoveris (450 IU + 225 IU)/0.72 mL solution for injection in pre-filled pen
Follitropin alfa/Lutropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 450 IU (equivalent to 33 micrograms) of follitropin alfa (r-hFSH) and 225 IU (equivalent to 9 micrograms) of lutropin alfa (r-hLH) in 0.72 mL.

3. LIST OF EXCIPIENTS

Excipients: sucrose, arginine monohydrochloride, poloxamer 188, methionine, phenol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide and concentrated phosphoric acid (for pH adjustment), and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 multidose pre-filled pen of 0.72 mL solution
7 injection needles

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once opened, the medicinal product may be stored for a maximum of 28 days at 25°C.
9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. 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 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/1/07/396/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pergoveris (450 iu + 225 iu)/0.72 ml pen

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

PERGOVERIS (450 IU + 225 IU)/0.72 ML SOLUTION FOR INJECTION IN PRE-FILLED PEN, PEN LABEL

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

Pergoveris (450 IU + 225 IU)/0.72 mL injection
Follitropin alfa/Lutropin alfa
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP
Shelf life after first use: 28 days

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

450 IU r-hFSH-225 IU r-hLH/0.72 mL

6. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PERGOVERIS (900 IU + 450 IU)/1.44 ML SOLUTION FOR INJECTION IN PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT
Pergoveris (900 IU + 450 IU)/1.44 mL solution for injection in pre-filled pen
Follitropin alfa/Lutropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each pre-filled pen contains 900 IU (equivalent to 66 micrograms) of follitropin alfa (r-hFSH) and 450 IU (equivalent to 18 micrograms) of lutropin alfa (r-hLH) in 1.44 mL.

3. LIST OF EXCIPIENTS
Excipients: sucrose, arginine monohydrochloride, poloxamer 188, methionine, phenol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide and concentrated phosphoric acid (for pH adjustment), and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS
Solution for injection
1 multidose pre-filled pen of 1.44 mL solution
14 injection needles

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 REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP
Once opened, the medicinal product may be stored for a maximum of 28 days at 25°C.
9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. 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 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/1/07/396/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pergoveris (900 iu + 450 iu)/1.44 ml pen

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

PERGOVERIS (900 IU + 450 IU)/1.44 ML SOLUTION FOR INJECTION IN PRE-FILLED PEN, PEN LABEL

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pergoveris (900 IU + 450 IU)/1.44 mL injection</td>
</tr>
<tr>
<td>Follitropin alfa/Lutropin alfa</td>
</tr>
<tr>
<td>Subcutaneous use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
<tr>
<td>Shelf life after first use: 28 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 IU r-hFSH- 450 IU r-hLH/1.44 mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
</table>
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, pharmacist or nurse 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 hyperstimulation syndrome (OHSS)**
This medicine stimulates your ovaries. This increases your risk of developing ovarian hyperstimulation syndrome (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 using, have recently used or might use 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.

Pergoveris contains sodium
Pergoveris contains less than 1 mmol sodium (23 mg) per dose, i.e. 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”.

63
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 a licensed follitropin alfa preparation 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 hyperstimulation syndrome (OHSS)"). 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 hyperstimulation syndrome (OHSS)”).

If you forget to use Pergoveris
Do not use 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 everybody 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 hyperstimulation syndrome (OHSS)
- Lower abdominal pain together with nausea or vomiting. These 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 in section 2. under “Ovarian hyperstimulation syndrome (OHSS)”). 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 in section 2. under “Blood clotting problems (thromboembolic events)”).

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, 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 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 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 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

- Sucrose, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, methionine, polysorbate 20, as well as concentrated phosphoric acid and sodium hydroxide for pH-adjustment.

**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 with a bromobutyl rubber stopper containing 150 IU (equivalent to 11 micrograms) of follitropin alfa and 75 IU (equivalent to 3 micrograms) of lutropin alfa.
- The solvent is a clear colourless liquid in a glass vial containing 1 mL of water for injections.
- 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**

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

**Manufacturer**

Merck Serono S.p.A, Via delle Magnolie 15 (Zona industriale), I-70026 Modugno (Bari), Italy
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
MERCK NV/SA  
Tél/Tel: +32-2-686 07 11

**Литва**
Merck Serono UAB  
Tel: +370 37320603

**България**
„Мерк България“ ЕАД  
Тел.: +359 24461 111

**Magyarország**
Merck Kft.  
Tel: +36-1-463-8100

**Česká republika**
Merck spol.s.r.o  
Tel. +420 272084211

**Malta**
Vivian Corporation Ltd  
Tel: +356-22-588600

**Danmark**
Merck A/S  
Tlf: +45 35253550

**Nederland**
Merck BV  
Tel: +31-20-6582800

**Deutschland**
Merck Serono GmbH  
Tel: +49-6151-6285-0

**Norge**
Merck Serono Norge  
Tlf: +47 67 90 35 90

**Ελλάδα**
Merck A.E.  
Τηλ.: +30-210-61 65 100

**Österreich**
Merck GesmbH.  
Tel: +43 1 57600-0

**España**
Merck S.L.  
Línea de Información: 900 102 964  
Tel: +34-91-745 44 00

**Polska**
Merck Sp. z o.o.  
Tel.: +48 22 53 59 700

**France**
Merck Serono s.a.s.  
Tél.: +33-4-72 78 25 25  
Numéro vert : 0 800 888 024

**Portugal**
Merck, s.a.  
Tel: +351-21-361 35 00

**Hrvatska**
Merck d.o.o,  
Tel: +385 1 4864 111

**România**
MERCK d.o.o., Slovenia  
Tel: +386 1 560 3 800

**Írland**
Merck Serono Ltd, United Kingdom  
Tel: +44-20 8818 7200

**Slovenija**
MERCK d.o.o.  
Tel: +386 1 560 3 800

**Ísland**
Icepharma hf  
Tel: + 354 540 8000

**Slovenská republika**
Merck spol. s r.o.  
Tel: + 421 2 49 267 111
This leaflet was last revised in {MM/YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicine Agency web site: http://www.ema.europa.eu.
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 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, pharmacist or nurse 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 hyperstimulation syndrome (OHSS)**
This medicine stimulates your ovaries. This increases your risk of developing ovarian hyperstimulation syndrome (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 using, have recently used or might use any other medicines.

Do not use Pergoveris with other medicines in the same injection. You can use Pergoveris with a licensed follitropin alfa preparation as separate injections, 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.

Pergoveris contains sodium
Pergoveris contains less than 1 mmol sodium (23 mg) per dose, i.e. 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.
- Your doctor or nurse will show you how to use the Pergoveris pre-filled pen to inject the medicine.
- If they are satisfied that you can administer Pergoveris safely, you can then prepare and inject the medicine yourself at home.
- If you administer Pergoveris to yourself, please carefully read and follow section “Instructions for Use”.
How much to use
A treatment regimen commences with the recommended dose of Pergoveris containing 150 International Units (IU) of follitropin alfa and 75 IU of lutropin alfa every day.

- According to your response, your doctor may decide to add every day a dose of a licensed follitropin alfa preparation 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 hyperstimulation syndrome (OHSS)”)). In this case, your doctor will give you a lower follitropin alfa dose in the following cycle.

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 hyperstimulation syndrome (OHSS)”).

If you forget to use Pergoveris
Do not use 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 everybody 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 hyperstimulation syndrome (OHSS)
- Lower abdominal pain together with nausea or vomiting. These 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 in section 2, under “Ovarian hyperstimulation syndrome (OHSS)”)). 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 in section 2. under “Blood clotting problems (thromboembolic events)”).

**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, 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 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 label and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C). Do not freeze.
Store in the original package in order to protect from light.

Once opened, the pre-filled pen may be stored for a maximum of 28 days outside of the refrigerator (at 25°C).

Do not use Pergoveris if you notice any visible signs of deterioration, if the liquid contains particles or is not clear.

After the injection, dispose of the used needle safely.

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 Pergoveris contains
The active substances are follitropin alfa and lutropin alfa.
- Each pre-filled pen of Pergoveris (300 IU + 150 IU)/0.48 mL contains 300 IU (International Units) of follitropin alfa and 150 IU of lutropin alfa in 0.48 mL and can deliver two doses of Pergoveris 150 IU/75 IU.

The other ingredients are
- Sucrose, arginine monohydrochloride, poloxamer 188, methionine, phenol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate and water for injections. Tiny amounts of concentrated phosphoric acid and sodium hydroxide are added to keep acidity levels (pH levels) normal.

What Pergoveris looks like and contents of the pack
Pergoveris is presented as a clear, colourless to slightly yellow solution for injection in a multidose pre-filled pen:
- Pergoveris (300 IU + 150 IU)/0.48 mL is supplied in packs of 1 multidose pre-filled pen and 5 disposable injection needles.

Marketing Authorisation Holder
Merck Serono Europe Limited, 56 Marsh Wall, London E14 9TP, United Kingdom

Manufacturer
Merck Serono S.p.A, Via delle Magnolie 15 (Zona industriale), I-70026 Modugno (Bari), Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

<table>
<thead>
<tr>
<th>België/Belgique/Belgien</th>
<th>Lietuva</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERCK NV/SA</td>
<td>Merck Serono UAB</td>
</tr>
<tr>
<td>Tél/Tel: +32-2-686 07 11</td>
<td>Tel: +370 37320603</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>България</th>
</tr>
</thead>
<tbody>
<tr>
<td>„Мерк България“ ЕАД</td>
</tr>
<tr>
<td>Тел.: +359 24461 111</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Česká republika</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck spol.s.r.o</td>
</tr>
<tr>
<td>Tel. +420 272084211</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Danmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck A/S</td>
</tr>
<tr>
<td>Tlf: +45 35253550</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Deutschland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck Serono GmbH</td>
</tr>
<tr>
<td>Tel: +49-6151-6285-0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eesti</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck Serono OÜ</td>
</tr>
<tr>
<td>Tel: +372 682 5882</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nederland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck BV</td>
</tr>
<tr>
<td>Tel: +31-20-6582800</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vivian Corporation Ltd</td>
</tr>
<tr>
<td>Tel: +356-22-588600</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Norge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck Serono Norge</td>
</tr>
<tr>
<td>Tlf: +47 67 90 35 90</td>
</tr>
</tbody>
</table>
Other sources of information

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

Instructions for Use

Contents
1. Important information about the Pergoveris pre-filled pen
2. How to use your Pergoveris pre-filled pen treatment diary
3. Gathering your supplies
4. Getting familiar with the parts of your Pergoveris pre-filled pen
5. Getting your Pergoveris pre-filled pen ready for injection
6. Setting the dose prescribed by your doctor
7. Injecting the dose
8. After the injection
9. Pergoveris pre-filled pen treatment diary (See table at the end)

Warning: Please read these instructions for use before using your Pergoveris pre-filled pen. Follow the instructions exactly, as it may differ from your past experience.

1. Important information about the Pergoveris pre-filled pen

- The Pergoveris pre-filled pen is for subcutaneous injection only.
- Only use the Pergoveris pre-filled pen if your healthcare provider trains you on how to use it correctly.

Warning: Do not reuse needles. Remove the needle immediately after each injection. Do not share the pen and/or needles with another person, because doing so can cause an infection.
- The pen comes in 3 different multi-dose presentations:

(300 IU + 150 IU)/0.48 mL  
• Contains 0.48 mL of Pergoveris solution  
• Contains 300 IU follitropin alfa and 150 IU lutropin alfa.

(450 IU + 225 IU)/0.72 mL  
• Contains 0.72 mL of Pergoveris solution  
• Contains 450 IU follitropin alfa and 225 IU lutropin alfa.

(900 IU + 450 IU)/1.44 mL  
• Contains 1.44 mL of Pergoveris solution  
• Contains 900 IU follitropin alfa and 450 IU lutropin alfa.

Warning: Refer to the Package leaflet for more information on the recommended dose regimen and always follow the dose recommended by your doctor.

- The numbers in the Dose Feedback Window present the number of International Units, or IUs, and show the dose of follitropin alfa. Your doctor will tell you how many IUs of follitropin alfa to inject each day.
- The numbers displayed in the Dose Feedback Window help you to:
  a. Dial your prescribed dose.
b. Verify a complete injection.

![Image of Dose Feedback Window with 0]

c. Read the dose remaining to be injected with a second pen.

![Image of 150 IU in a pen]

- Give yourself the injection at the same time each day.
- Your doctor/pharmacist will tell you how many pens of Pergoveris you need to complete your treatment.

2. How to use your Pergoveris pre-filled pen treatment diary

A treatment diary is included on the last page. Use the treatment diary to record the amount injected.

- Record the treatment day number (column 1), date (column 2), time of your injection (column 3), and volume of your pen (column 4).
- Record your prescribed dose (column 5).
- Verify you dialed the right dose before injecting (column 6).
- After injection, read the number shown in the Dose Feedback Window.
- Confirm you received a complete injection (column 7) OR record the number shown in the Dose Feedback Window if other than “0” (column 8).
- When needed, inject yourself using a second pen, dialing your remaining dose written in the “Amount to Be Set for a Second Injection” section (column 8).
- Record this remaining dose in the “Amount Set to Inject” section in the next row (column 6).

**NOTE:** Using your treatment diary to record your daily injection(s) allows you to verify that you received the full prescribed dose every day.

An example of a treatment diary using a \((450 \text{ IU} + 225 \text{ IU})/0.72 \text{ mL}\) pen:

<table>
<thead>
<tr>
<th>1 Treatment Day Number</th>
<th>2 Date</th>
<th>3 Time</th>
<th>4 Pen Volume</th>
<th>5 Prescribed Dose</th>
<th>6 Dose Feedback Window</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#1</td>
<td>10/06</td>
<td>19:00</td>
<td>450IU+225IU</td>
<td>150</td>
<td>&quot;0&quot;, injection complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>if not &quot;0&quot;, need second injection Inject this amount using new pen</td>
</tr>
<tr>
<td>#2</td>
<td>11/06</td>
<td>19:00</td>
<td>450IU+225IU</td>
<td>150</td>
<td>&quot;0&quot;, injection complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>if not &quot;0&quot;, need second injection Inject this amount using new pen</td>
</tr>
<tr>
<td>#3</td>
<td>12/06</td>
<td>19:00</td>
<td>450IU+225IU</td>
<td>225</td>
<td>&quot;0&quot;, injection complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>if not &quot;0&quot;, need second injection Inject this amount 75 using new pen</td>
</tr>
<tr>
<td>#3</td>
<td>12/06</td>
<td>19:00</td>
<td>450IU+225IU</td>
<td>N/A</td>
<td>&quot;0&quot;, injection complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>if not &quot;0&quot;, need second injection Inject this amount using new pen</td>
</tr>
</tbody>
</table>
3. Gathering your supplies

3.1. Wash your hands with soap and water (Fig. 1).

3.2. Prepare a clean area and a flat surface, such as a table or countertop, in a well-lit area.

3.3. Select your Pergoveris pre-filled pen.

3.4. Verify you select the prescribed pen.

3.5. Verify the expiration date on the pen label (Fig. 2).

3.6. You will also need:
   - Needles (included in the pack)
   - Alcohol swabs (not included in the pack)
   - A sharps disposal bin (not included in the pack)

4. Getting familiar with the parts of your Pergoveris pre-filled pen

* The numbers on the Dose Feedback Window and reservoir holder represent the number of International Units (IU) of medication.
5. Getting your Pergoveris pre-filled pen ready for injection

5.1. Take off the pen cap.
5.2. Verify that the Dose Feedback Window is set to "0".

5.3. Prepare your needle.

- Get a new needle - only use the "single-use" needles supplied.
- Hold the outer needle cap firmly.
- Check that the peel-off seal on the outer needle cap is not damaged or loose (Fig. 3).

- Remove the peel-off seal (Fig. 4).

**Caution:** If the peel-off seal is damaged or loose, do not use the needle. Throw it away in a sharps disposal container. Get a new needle.

5.4. Attach the needle.

- Screw the threaded tip of the Pergoveris pre-filled pen into the outer needle cap until you feel a light resistance.

**Caution:** Do not attach the needle too tightly; the needle could be difficult to remove after the injection.
- Remove the outer needle cap by pulling it gently.

- **Put it aside for later use. DO NOT discard it.**
- Hold the Pergoveris pre-filled pen with the needle pointing upward.
- Carefully remove and discard the green inner shield.

**Warning:** Do not recap the needle with the green inner shield, as it can lead to needle stick.
5.5. Check for a droplet of liquid at the tip of the needle.
   • Look closely at the tip of the needle for tiny drop(s) of fluid.

<table>
<thead>
<tr>
<th>IF</th>
<th>THEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using a new pen</td>
<td>Check for a droplet of liquid at the tip of the needle.</td>
</tr>
<tr>
<td></td>
<td>• If you see a droplet, proceed to Section 6: Setting the dose</td>
</tr>
<tr>
<td></td>
<td>prescribed by your doctor.</td>
</tr>
<tr>
<td></td>
<td>• If no droplet is seen, follow the instructions on the following</td>
</tr>
<tr>
<td></td>
<td>page.</td>
</tr>
<tr>
<td>Reusing a pen</td>
<td>It is NOT required to check for a droplet of liquid.</td>
</tr>
<tr>
<td></td>
<td>Proceed directly to Section 6: Setting the dose prescribed by your</td>
</tr>
<tr>
<td></td>
<td>doctor.</td>
</tr>
</tbody>
</table>

If you do not see a tiny drop(s) of fluid at or near the tip the first time you use a new pen:

1. Gently turn the dose setting knob clockwise until it reads 25 in the Dose Feedback Window. You can turn the dose knob backwards if you turn it past 25 (Fig. 5).

2. Hold the pen with the needle pointing upward.
3. Tap the reservoir holder gently (Fig. 6).
4. Press the dose setting knob as far as it will go. A tiny drop of liquid will appear at the tip of the needle (Fig. 7).
5. Verify that the Dose Feedback Window reads "0" (Fig. 8).
6. Proceed to Section 6: Setting the dose prescribed by your doctor.
6. Setting the dose prescribed by your doctor

6.1. Turn the dose setting knob until your intended dose shows in the Dose Feedback Window.

- Turn the dose setting knob forward to dial up according to the dose that was prescribed by your doctor.

- If needed, turn the dose setting knob backward to correct the dose.

**Warning:** Check that the **Dose Feedback Window** displays your **complete prescribed dose** before you move on to the next step.

7. Injecting the dose

7.1. Choose an injection site in the area your doctor or nurse has told you to use for the injection. To minimize skin irritation, select a different injection site each day.

7.2. Wipe the skin with an alcohol swab.

7.3. Verify once more that the **Dose Feedback Window** displays the correct dose.

7.4. Inject the dose as you were trained to do by your doctor or nurse.

- Slowly push the needle into the skin entirely (Fig. 9).
- **Slowly press the dose knob down as far as it will go** and hold it to complete the full injection.

- Hold the dose knob down for a minimum of 5 seconds to ensure you inject the full dose (Fig. 10).
- The dose number shown in the **Dose Feedback Window** will turn back to 0.

- After a minimum of 5 seconds, pull the needle out of the skin while keeping the dose setting knob pressed down (Fig. 11).
- When the needle is out of the skin, release the dose setting knob.

**Caution:** Do not release the dose knob until you remove the needle from the skin.
Warning: Always make sure to use a new needle for each injection.

8. After the injection

8.1. Verify you have given a complete injection.

- Check that the Dose Feedback Window shows “0”.

Warning: If the Dose Feedback Window shows a number higher than 0, the Pergoveris pre-filled pen is empty and you have not received your full prescribed dose.

8.2. Complete a partial injection (only when needed).

- The Dose Feedback Window will indicate the missing amount you need to inject using a new pen.

- Repeat Section 4 (Getting familiar with your Pergoveris pre-filled pen) through Section 5 (Getting your Pergoveris pre-filled pen ready for injection) with a second pen.

- Set the dose to the missing amount you recorded in the treatment diary OR the number still displayed in the Dose Feedback Window on your previous pen, and inject.

8.3. Removing the needle after each injection.

- Place the outer needle cap on a flat surface.
- Hold the Pergoveris pre-filled pen firmly with one hand, and slip the needle into the outer needle cap.

- Continue by pushing the capped needle against a firm surface until you hear a “click”.

- Grip the outer needle cap and unscrew the needle by turning anti-clockwise. Dispose of the used needle safely.
- Recap the pen.

Warning: Never reuse any used needle. Never share needles.

8.4. Storing the Pergoveris pre-filled pen.

Caution: Never store the pen with the needle still attached. Always remove the needle from the Pergoveris pre-filled pen before replacing the pen cap.

- Store the pen in its original packaging in a safe place and as indicated in the package leaflet.
When the pen is empty, ask your pharmacist how to dispose of it.

**Warning:** Medicine should not be disposed of via wastewater or household waste.

### 9. Pergoveris pre-filled pen treatment diary

<table>
<thead>
<tr>
<th>1 Treatment Day Number</th>
<th>2 Date</th>
<th>3 Time</th>
<th>4 Pen Volume</th>
<th>5 Prescribed Dose</th>
<th>6 Amount Set to Inject</th>
<th>7 Amount to Be Set for a Second Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>

This instructions for use was last revised in:
Package leaflet: Information for the user
Pergoveris (450 IU + 225 IU)/0.72 mL solution for injection in pre-filled pen
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, 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 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, pharmacist or nurse 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 hyperstimulation syndrome (OHSS)**

This medicine stimulates your ovaries. This increases your risk of developing ovarian hyperstimulation syndrome (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 using, have recently used or might use any other medicines.

Do not use Pergoveris with other medicines in the same injection. You can use Pergoveris with a licensed follitropin alfa preparation as separate injections, 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.

Pergoveris contains sodium
Pergoveris contains less than 1 mmol sodium (23 mg) per dose, i.e. 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.
- Your doctor or nurse will show you how to use the Pergoveris pre-filled pen to inject the medicine.
- If they are satisfied that you can administer Pergoveris safely, you can then prepare and inject the medicine yourself at home.
- If you administer Pergoveris to yourself, please carefully read and follow section “Instructions for Use”.
How much to use
A treatment regimen commences with the recommended dose of Pergoveris containing 150 International Units (IU) of follitropin alfa and 75 IU of lutropin alfa every day.
- According to your response, your doctor may decide to add every day a dose of a licensed follitropin alfa preparation 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 hyperstimulation syndrome (OHSS)”). In this case, your doctor will give you a lower follitropin alfa dose in the following cycle.

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 hyperstimulation syndrome (OHSS)”).

If you forget to use Pergoveris
Do not use 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 everybody 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 hyperstimulation syndrome (OHSS)
- Lower abdominal pain together with nausea or vomiting. These 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 in section 2. under “Ovarian hyperstimulation syndrome (OHSS)”). 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 in section 2. under “Blood clotting problems (thromboembolic events)”).

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, 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 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 label and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C). Do not freeze.
Store in the original package in order to protect from light.

Once opened, the pre-filled pen may be stored for a maximum of 28 days outside of the refrigerator (at 25°C).

Do not use Pergoveris if you notice any visible signs of deterioration, if the liquid contains particles or is not clear.

After the injection, dispose of the used needle safely.

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 Pergoveris contains
The active substances are follitropin alfa and lutropin alfa.
• Each pre-filled pen of Pergoveris (450 IU + 225 IU)/0.72 mL contains 450 IU (International Units) of follitropin alfa and 225 IU of lutropin alfa in 0.72 mL and can deliver three doses of Pergoveris 150 IU/75 IU.

The other ingredients are
• Sucrose, arginine monohydrochloride, poloxamer 188, methionine, phenol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate and water for injections. Tiny amounts of concentrated phosphoric acid and sodium hydroxide are added to keep acidity levels (pH levels) normal.

What Pergoveris looks like and contents of the pack
Pergoveris is presented as a clear, colourless to slightly yellow solution for injection in a multidose pre-filled pen:
• Pergoveris (450 IU + 225 IU)/0.72 mL is supplied in packs of 1 multidose pre-filled pen and 7 disposable injection needles.

Marketing Authorisation Holder
Merck Serono Europe Limited, 56 Marsh Wall, London E14 9TP, United Kingdom

Manufacturer
Merck Serono S.p.A, Via delle Magnolie 15 (Zona industriale), I-70026 Modugno (Bari), Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
MERCK NV/SA
Tél/Tel: +32-2-686 07 11

**България**
„Мерк България“ ЕАД
Тел.: +359 24461 111

**Česká republika**
Merck spol.s.r.o
Tel. +420 272084211

**Danmark**
Merck A/S
Tlf: +45 35253550

**Deutschland**
Merck Serono GmbH
Tel: +49-6151-6285-0

**Eesti**
Merck Serono OÜ
Tel: +372 682 5882

**Lietuva**
Merck Serono UAB
Tel: +370 37320603

**Luxembourg/Luxemburg**
MERCK NV/SA, Belgique/Belgien
Tél/Tel: +32-2-686 07 11

**Magyarország**
Merck Kft.
Tel: +36-1-463-8100

**Malta**
Vivian Corporation Ltd
Tel: +356-22-588600

**Nederland**
Merck BV
Tel: +31-20-6582800

**Norge**
Merck Serono Norge
Tlf: +47 67 90 35 90
This leaflet was last revised in {MM/YYYY}.

Other sources of information

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

Instructions for Use

Contents
1. Important information about the Pergoveris pre-filled pen
2. How to use your Pergoveris pre-filled pen treatment diary
3. Gathering your supplies
4. Getting familiar with the parts of your Pergoveris pre-filled pen
5. Getting your Pergoveris pre-filled pen ready for injection
6. Setting the dose prescribed by your doctor
7. Injecting the dose
8. After the injection
9. Pergoveris pre-filled pen treatment diary (See table at the end)

Warning: Please read these instructions for use before using your Pergoveris pre-filled pen. Follow the instructions exactly, as it may differ from your past experience.

1. Important information about the Pergoveris pre-filled pen

- The Pergoveris pre-filled pen is for subcutaneous injection only.
- Only use the Pergoveris pre-filled pen if your healthcare provider trains you on how to use it correctly.

Warning: Do not reuse needles. Remove the needle immediately after each injection. Do not share the pen and/or needles with another person, because doing so can cause an infection.

- The pen comes in 3 different multi-dose presentations:

  - (300 IU + 150 IU)/0.48 mL: Contains 0.48 mL of Pergoveris solution
  - Contains 300 IU follitropin alfa and 150 IU lutropin alfa.

  - (450 IU + 225 IU)/0.72 mL: Contains 0.72 mL of Pergoveris solution
  - Contains 450 IU follitropin alfa and 225 IU lutropin alfa.

  - (900 IU + 450 IU)/1.44 mL: Contains 1.44 mL of Pergoveris solution
  - Contains 900 IU follitropin alfa and 450 IU lutropin alfa.

Warning: Refer to the Package leaflet for more information on the recommended dose regimen and always follow the dose recommended by your doctor.

- The numbers in the Dose Feedback Window present the number of International Units, or IUs, and show the dose of follitropin alfa. Your doctor will tell you how many IUs of follitropin alfa to inject each day.

- The numbers displayed in the Dose Feedback Window help you to:
  
  a. Dial your prescribed dose.
b. Verify a complete injection.

![Image of Dose Feedback Window]

0

\[ 0 \]

\[ 150 \]

c. Read the dose remaining to be injected with a second pen.

![Image of Dose Feedback Window]

\[ 150 \]

- Give yourself the injection at the same time each day.
- Your doctor/pharmacist will tell you how many pens of Pergoveris you need to complete your treatment.

2. How to use your Pergoveris pre-filled pen treatment diary

A treatment diary is included on the last page. Use the treatment diary to record the amount injected.

- Record the treatment day number (column 1), date (column 2), time of your injection (column 3), and volume of your pen (column 4).
- Record your prescribed dose (column 5).
- Verify you dialed the right dose before injecting (column 6).
- After injection, read the number shown in the Dose Feedback Window.
- Confirm you receive a complete injection (column 7) OR record the number shown in the Dose Feedback Window if other than ‘0’ (column 8).
- When needed, inject yourself using a second pen, dialing your remaining dose written in the “Amount to Be Set for a Second Injection” section (column 8).
- Record this remaining dose in the “Amount Set to Inject” section in the next row (column 6).

**NOTE:** Using your treatment diary to record your daily injection(s) allows you to verify that you received the full prescribed dose every day.

An example of a treatment diary using a \((450 \text{ IU} + 225 \text{ IU})/0.72 \text{ mL}\) pen:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Day Number</td>
<td>Date</td>
<td>Time</td>
<td>Pen Volume</td>
<td>Prescribed Dose</td>
<td>Amount Set to Inject</td>
<td>Amount to Be Set for a Second Injection</td>
<td></td>
</tr>
<tr>
<td>#1</td>
<td>10/06</td>
<td>1900</td>
<td>450IU/225IU</td>
<td>150IU/75IU</td>
<td>150IU/75IU</td>
<td>if “0”, injection complete</td>
<td></td>
</tr>
<tr>
<td>#2</td>
<td>11/06</td>
<td>1900</td>
<td>450IU/225IU</td>
<td>150IU/75IU</td>
<td>150IU/75IU</td>
<td>if “0”, injection complete</td>
<td></td>
</tr>
<tr>
<td>#3</td>
<td>12/06</td>
<td>1900</td>
<td>450IU/225IU</td>
<td>225IU/112.5IU</td>
<td>225IU/112.5IU</td>
<td>if “0”, injection complete</td>
<td></td>
</tr>
<tr>
<td>#3</td>
<td>12/06</td>
<td>1900</td>
<td>450IU/225IU</td>
<td>N/A</td>
<td>75IU</td>
<td>if “0”, injection complete</td>
<td></td>
</tr>
<tr>
<td>#3</td>
<td>12/06</td>
<td>1900</td>
<td>450IU/225IU</td>
<td>N/A</td>
<td>75IU</td>
<td>if “0”, injection complete</td>
<td></td>
</tr>
</tbody>
</table>

450 IU + 225 IU/0.72 mL pen
3. **Gathering your supplies**

3.1. Wash your hands with soap and water (Fig. 1).

3.2. Prepare a **clean area** and a **flat surface**, such as a table or countertop, in a well-lit area.

3.3. Select your Pergoveris pre-filled pen.

3.4. Verify you select the prescribed pen.

3.5. Verify the **expiration date** on the pen label (Fig. 2).

3.6. You will also need:
- Needles (included in the pack)
- Alcohol swabs (not included in the pack)
- A sharps disposal bin (not included in the pack)

4. **Getting familiar with the parts of your Pergoveris pre-filled pen**

* The numbers on the **Dose Feedback Window** and reservoir holder represent the number of International Units (IU) of medication.
5. Getting your Pergoveris pre-filled pen ready for injection

5.1. Take off the pen cap.
5.2. Verify that the Dose Feedback Window is set to "0".

5.3. Prepare your needle.

- Get a new needle - only use the "single-use" needles supplied.
- Hold the outer needle cap firmly.
- Check that the peel-off seal on the outer needle cap is not damaged or loose (Fig.3).

- Remove the peel-off seal (Fig. 4).

**Caution:** If the peel-off seal is damaged or loose, do not use the needle. Throw it away in a sharps disposal container. Get a new needle.

5.4. Attach the needle.

- Screw the threaded tip of the Pergoveris pre-filled pen into the outer needle cap until you feel a light resistance.

**Caution:** Do not attach the needle too tightly; the needle could be difficult to remove after the injection.
- Remove the outer needle cap by pulling it gently.
- **Put it aside for later use. DO NOT discard it.**
- Hold the Pergoveris pre-filled pen with the needle pointing upward.
- Carefully remove and discard the green inner shield.

**Warning:** Do not recap the needle with the green inner shield, as it can lead to needle stick.
5.5. Check for a droplet of liquid at the tip of the needle.
- Look closely at the tip of the needle for tiny drop(s) of fluid.

<table>
<thead>
<tr>
<th>IF</th>
<th>THEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using a new pen</td>
<td>Check for a droplet of liquid at the tip of the needle.</td>
</tr>
<tr>
<td></td>
<td>• If you see a droplet, proceed to Section 6: Setting the dose</td>
</tr>
<tr>
<td></td>
<td>prescribed by your doctor.</td>
</tr>
<tr>
<td></td>
<td>• If no droplet is seen, follow the instructions on the following page.</td>
</tr>
<tr>
<td>Reusing a pen</td>
<td>It is NOT required to check for a droplet of liquid.</td>
</tr>
<tr>
<td></td>
<td>Proceed directly to Section 6: Setting the dose prescribed by your doctor.</td>
</tr>
</tbody>
</table>

If you do not see a tiny drop(s) of fluid at or near the tip the first time you use a new pen:

1. Hold the pen with the needle pointing upward.
2. Tap the reservoir holder gently (Fig. 6).
3. Press the dose setting knob as far as it will go. A tiny drop of liquid will appear at the tip of the needle (Fig. 7).
4. Verify that the Dose Feedback Window reads "0" (Fig. 8).
5. Proceed to Section 6: Setting the dose prescribed by your doctor.
6. Setting the dose prescribed by your doctor

6.1. Turn the dose setting knob until your intended dose shows in the Dose Feedback Window.

- Turn the dose setting knob forward to dial up according to the dose that was prescribed by your doctor.

- If needed, turn the dose setting knob backward to correct the dose.

Warning: Check that the Dose Feedback Window displays your complete prescribed dose before you move on to the next step.

7. Injecting the dose

7.1. Choose an injection site in the area your doctor or nurse has told you to use for the injection. To minimize skin irritation, select a different injection site each day.

7.2. Wipe the skin with an alcohol swab.

7.3. Verify once more that the Dose Feedback Window displays the correct dose.

7.4. Inject the dose as you were trained to do by your doctor or nurse.

- Slowly push the needle into the skin entirely (Fig. 9).

- Slowly press the dose knob down as far as it will go and hold it to complete the full injection.

- Hold the dose knob down for a minimum of 5 seconds to ensure you inject the full dose (Fig. 10).

- The dose number shown in the Dose Feedback Window will turn back to 0.

- After a minimum of 5 seconds, pull the needle out of the skin while keeping the dose setting knob pressed down (Fig. 11).

- When the needle is out of the skin, release the dose setting knob.

Caution: Do not release the dose knob until you remove the needle from the skin.
Warning: Always make sure to use a new needle for each injection.

8. After the injection

8.1. Verify you have given a complete injection.
   • Check that the Dose Feedback Window shows “0”.

Warning: If the Dose Feedback Window shows a number higher than 0, the Pergoveris pre-filled pen is empty and you have not received your full prescribed dose.

8.2. Complete a partial injection (only when needed).
   • The Dose Feedback Window will indicate the missing amount you need to inject using a new pen.
   • Repeat Section 4 (Getting familiar with your Pergoveris pre-filled pen) through Section 5 (Getting your Pergoveris pre-filled pen ready for injection) with a second pen.
   • Set the dose to the missing amount you recorded in the treatment diary OR the number still displayed in the Dose Feedback Window on your previous pen, and inject.

8.3. Removing the needle after each injection.
   • Place the outer needle cap on a flat surface.
   • Hold the Pergoveris pre-filled pen firmly with one hand, and slip the needle into the outer needle cap.
   • Continue by pushing the capped needle against a firm surface until you hear a “click”.
   • Grip the outer needle cap and unscrew the needle by turning anti-clockwise. Dispose of the used needle safely.
   • Recap the pen.

Warning: Never reuse any used needle. Never share needles.

8.4. Storing the Pergoveris pre-filled pen.

Caution: Never store the pen with the needle still attached. Always remove the needle from the Pergoveris pre-filled pen before replacing the pen cap.

• Store the pen in its original packaging in a safe place and as indicated in the package leaflet.
When the pen is empty, ask your pharmacist how to dispose of it.

**Warning:** Medicine should not be disposed of via wastewater or household waste.

### 9. Pergoveris pre-filled pen treatment diary

<table>
<thead>
<tr>
<th>1 Treatment Day Number</th>
<th>2 Date</th>
<th>3 Time</th>
<th>4 Pen Volume</th>
<th>5 Prescribed Dose</th>
<th>6 Dose Feedback Window</th>
<th>7 Amount Set to Inject</th>
<th>8 Amount to Be Set for a Second Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f if &quot;0&quot;, injection complete if not &quot;0&quot;, second injection Inject this amount .... using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f if &quot;0&quot;, injection complete if not &quot;0&quot;, second injection Inject this amount .... using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f if &quot;0&quot;, injection complete if not &quot;0&quot;, second injection Inject this amount .... using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f if &quot;0&quot;, injection complete if not &quot;0&quot;, second injection Inject this amount .... using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f if &quot;0&quot;, injection complete if not &quot;0&quot;, second injection Inject this amount .... using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f if &quot;0&quot;, injection complete if not &quot;0&quot;, second injection Inject this amount .... using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f if &quot;0&quot;, injection complete if not &quot;0&quot;, second injection Inject this amount .... using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f if &quot;0&quot;, injection complete if not &quot;0&quot;, second injection Inject this amount .... using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f if &quot;0&quot;, injection complete if not &quot;0&quot;, second injection Inject this amount .... using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f if &quot;0&quot;, injection complete if not &quot;0&quot;, second injection Inject this amount .... using new pen</td>
</tr>
</tbody>
</table>

This instructions for use was last revised in:
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 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, pharmacist or nurse 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 hyperstimulation syndrome (OHSS)**
This medicine stimulates your ovaries. This increases your risk of developing ovarian hyperstimulation syndrome (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 using, have recently used or might use any other medicines.

Do not use Pergoveris with other medicines in the same injection. You can use Pergoveris with a licensed follitropin alfa preparation as separate injections, 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.

Pergoveris contains sodium
Pergoveris contains less than 1 mmol sodium (23 mg) per dose, i.e. 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.
• Your doctor or nurse will show you how to use the Pergoveris pre-filled pen to inject the medicine.
• If they are satisfied that you can administer Pergoveris safely, you can then prepare and inject the medicine yourself at home.
• If you administer Pergoveris to yourself, please carefully read and follow section “Instructions for Use”.

102
How much to use
A treatment regimen commences with the recommended dose of Pergoveris containing 150 International Units (IU) of follitropin alfa and 75 IU of lutropin alfa every day.

- According to your response, your doctor may decide to add every day a dose of a licensed follitropin alfa preparation 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 hyperstimulation syndrome (OHSS)”). In this case, your doctor will give you a lower follitropin alfa dose in the following cycle.

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 hyperstimulation syndrome (OHSS)”).

If you forget to use Pergoveris
Do not use 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 everybody 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 hyperstimulation syndrome (OHSS)

- Lower abdominal pain together with nausea or vomiting. These 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 in section 2. under “Ovarian hyperstimulation syndrome (OHSS)”). 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 in section 2. under “Blood clotting problems (thromboembolic events)”).

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, 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 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 label and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C). Do not freeze.
Store in the original package in order to protect from light.

Once opened, the pre-filled pen may be stored for a maximum of 28 days outside of the refrigerator (at 25°C).

Do not use Pergoveris if you notice any visible signs of deterioration, if the liquid contains particles or is not clear.

After the injection, dispose of the used needle safely.

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 Pergoveris contains
The active substances are follitropin alfa and lutropin alfa.
- Each pre-filled pen of Pergoveris (900 IU + 450 IU)/1.44 mL contains 900 IU (International Units) of follitropin alfa and 450 IU of lutropin alfa in 1.44 mL and can deliver six doses of Pergoveris 150 IU/75 IU.

The other ingredients are
- Sucrose, arginine monohydrochloride, poloxamer 188, methionine, phenol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate and water for injections. Tiny amounts of concentrated phosphoric acid and sodium hydroxide are added to keep acidity levels (pH levels) normal.

What Pergoveris looks like and contents of the pack
Pergoveris is presented as a clear, colourless to slightly yellow solution for injection in a multidose pre-filled pen:
- Pergoveris (900 IU + 450 IU)/1.44 mL is supplied in packs of 1 multidose pre-filled pen and 14 disposable injection needles.

Marketing Authorisation Holder
Merck Serono Europe Limited, 56 Marsh Wall, London E14 9TP, United Kingdom

Manufacturer
Merck Serono S.p.A, Via delle Magnolie 15 (Zona industriale), I-70026 Modugno (Bari), Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:
Ελλάδα
Merck A.E.
Τηλ.: +30-210-61 65 100

Österreich
Merck GesmbH.
Tel: +43 1 57600-0

España
Merck S.L.
Línea de Información: 900 102 964
Tel: +34-91-745 44 00

Polska
Merck Sp. z o.o.
Tel.: +48 22 53 59 700

France
Merck Serono s.a.s.
Tél.: +33-4-72 78 25 25
Numéro vert : 0 800 888 024

Portugal
Merck, s.a.
Tel: +351-21-361 35 00

Hrvatska
Merck d.o.o,
Tel: +385 1 4864 111

România
MERCK d.o.o., Slovenia
Tel: +386 1 560 3 800

Ýreland
Merck Serono Ltd, United Kingdom
Tel: +44-20 8818 7200

Slovenija
MERCK d.o.o.
Tel: +386 1 560 3 800

Ísland
Icepharma hf
Tel: + 354 540 8000

Slovenská republika
Merck spol. s r.o.
Tel: + 421 2 49 267 111

Italia
Merck Serono S.p.A.
Tel: +39-06-70 38 41

Suomi/Finland
Merck Oy
Puh/Tel: +358-9-8678 700

Κύπρος
Χρ. Γ. Παπαλοϊζου Λτδ
Τηλ.: +357 22490305

Sverige
Merck AB
Tel: +46-8-562 445 00

Latvija
Merck Serono SIA
Tel: +371 67152500

United Kingdom
Merck Serono Ltd
Tel: +44-20 8818 7200

This leaflet was last revised in {MM/YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicine Agency web site:
Pergoveris pre-filled pen

Instructions for Use

Contents
1. Important information about the Pergoveris pre-filled pen
2. How to use your Pergoveris pre-filled pen treatment diary
3. Gathering your supplies
4. Getting familiar with the parts of your Pergoveris pre-filled pen
5. Getting your Pergoveris pre-filled pen ready for injection
6. Setting the dose prescribed by your doctor
7. Injecting the dose
8. After the injection
9. Pergoveris pre-filled pen treatment diary (See table at the end)

Warning: Please read these instructions for use before using your Pergoveris pre-filled pen. Follow the instructions exactly, as it may differ from your past experience.

1. Important information about the Pergoveris pre-filled pen

- The Pergoveris pre-filled pen is for subcutaneous injection only.
- Only use the Pergoveris pre-filled pen if your healthcare provider trains you on how to use it correctly.

Warning: Do not reuse needles. Remove the needle immediately after each injection.

Do not share the pen and/or needles with another person, because doing so can cause an infection.
- The pen comes in 3 different multi-dose presentations:

(300 IU + 150 IU)/0.48 mL
- Contains 0.48 mL of Pergoveris solution
- Contains 300 IU follitropin alfa and 150 IU lutropin alfa.

(450 IU + 225 IU)/0.72 mL
- Contains 0.72 mL of Pergoveris solution
- Contains 450 IU follitropin alfa and 225 IU lutropin alfa.

(900 IU + 450 IU)/1.44 mL
- Contains 1.44 mL of Pergoveris solution
- Contains 900 IU follitropin alfa and 450 IU lutropin alfa.

Warning: Refer to the Package leaflet for more information on the recommended dose regimen and always follow the dose recommended by your doctor.

- The numbers in the Dose Feedback Window present the number of International Units, or IUs, and show the dose of follitropin alfa. Your doctor will tell you how many IUs of follitropin alfa to inject each day.
- The numbers displayed in the Dose Feedback Window help you to:
  a. Dial your prescribed dose.
b. Verify a complete injection.

![Image](image1)

c. Read the dose remaining to be injected with a second pen.

![Image](image2)

- Give yourself the injection at the same time each day.
- Your doctor/pharmacist will tell you how many pens of Pergoveris you need to complete your treatment.

2. How to use your Pergoveris pre-filled pen treatment diary

A treatment diary is included on the last page. Use the treatment diary to record the amount injected.

- Record the treatment day number (column 1), date (column 2), time of your injection (column 3), and volume of your pen (column 4).
- Record your prescribed dose (column 5).
- Verify you dialed the right dose before injecting (column 6).
- After injection, read the number shown in the Dose Feedback Window.
- Confirm you receive a complete injection (column 7) OR record the number shown in the Dose Feedback Window if other than ‘0’ (column 8).
- When needed, inject yourself using a second pen, dialing your remaining dose written in the “Amount to Be Set for a Second Injection” section (column 8).
- Record this remaining dose in the “Amount Set to Inject” section in the next row (column 6).

NOTE: Using your treatment diary to record your daily injection(s) allows you to verify that you received the full prescribed dose every day.

An example of a treatment diary using a \((450 \text{ IU} + 225 \text{ IU})/0.72 \text{ mL}\) pen:

<table>
<thead>
<tr>
<th>Treatment Day</th>
<th>2 Date</th>
<th>3 Time</th>
<th>4 Pen Volume</th>
<th>5 Prescribed Dose</th>
<th>6 Amount to Inject</th>
<th>7 Dose Feedback Window</th>
<th>8 Amount to Be Set for a Second Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 10/06</td>
<td>19:00</td>
<td>450IU+225IU</td>
<td>150IU/75IU</td>
<td>150</td>
<td></td>
<td>if &quot;0&quot;, injection complete</td>
<td>if not &quot;0&quot;, need second injection Inject this amount ......using new pen</td>
</tr>
<tr>
<td>#2 11/06</td>
<td>19:00</td>
<td>450IU+225IU</td>
<td>150IU/75IU</td>
<td>150</td>
<td></td>
<td>if &quot;0&quot;, injection complete</td>
<td>if not &quot;0&quot;, need second injection Inject this amount ......using new pen</td>
</tr>
<tr>
<td>#3 12/06</td>
<td>19:00</td>
<td>450IU+225IU</td>
<td>225IU/112.5IU</td>
<td>225</td>
<td></td>
<td>if &quot;0&quot;, injection complete</td>
<td>if not &quot;0&quot;, need second injection Inject this amount .75 using new pen</td>
</tr>
<tr>
<td>#3 12/06</td>
<td>19:00</td>
<td>450IU+225IU</td>
<td>N/A</td>
<td>75</td>
<td></td>
<td>if &quot;0&quot;, injection complete</td>
<td>if not &quot;0&quot;, need second injection Inject this amount ......using new pen</td>
</tr>
</tbody>
</table>
3. **Gathering your supplies**

3.1. Wash your hands with soap and water (Fig. 1).

3.2. Prepare a **clean area** and a **flat surface**, such as a table or countertop, in a well-lit area.

3.3. Select your Pergoveris pre-filled pen.

3.4. Verify you select the prescribed pen.

3.5. Verify the **expiration date** on the pen label (Fig. 2).

3.6. You will also need:
   - Needles (included in the pack)
   - Alcohol swabs (not included in the pack)
   - A sharps disposal bin (not included in the pack)

4. **Getting familiar with the parts of your Pergoveris pre-filled pen**

![Diagram of Pergoveris pre-filled pen with labels](image)

* The numbers on the **Dose Feedback Window** and reservoir holder represent the number of International Units (IU) of medication.
5. Getting your Pergoveris pre-filled pen ready for injection

5.1. Take off the pen cap.
5.2. Verify that the Dose Feedback Window is set to "0".

5.3. Prepare your needle.

- Get a new needle - only use the "single-use" needles supplied.
- Hold the outer needle cap firmly.
- Check that the peel-off seal on the outer needle cap is not damaged or loose (Fig.3).

- Remove the peel-off seal (Fig. 4).

**Caution:** If the peel-off seal is damaged or loose, do not use the needle. Throw it away in a sharps disposal container. Get a new needle.

5.4. Attach the needle.

- Screw the threaded tip of the Pergoveris pre-filled pen into the outer needle cap until you feel a light resistance.

**Caution:** Do not attach the needle too tightly; the needle could be difficult to remove after the injection.
- Remove the outer needle cap by pulling it gently.
- **Put it aside for later use. DO NOT discard it.**
- Hold the Pergoveris pre-filled pen with the needle pointing upward.
- Carefully remove and discard the green inner shield.

**Warning:** Do not recap the needle with the green inner shield, as it can lead to needle stick.
5.5. Check for a droplet of liquid at the tip of the needle.
- Look closely at the tip of the needle for tiny drop(s) of fluid.

<table>
<thead>
<tr>
<th>IF</th>
<th>THEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using a new pen</td>
<td>Check for a droplet of liquid at the tip of the needle.</td>
</tr>
<tr>
<td></td>
<td>- If you see a droplet, proceed to Section 6: Setting the dose prescribed by your doctor.</td>
</tr>
<tr>
<td></td>
<td>- If no droplet is seen, follow the instructions on the following page.</td>
</tr>
<tr>
<td>Reusing a pen</td>
<td>It is NOT required to check for a droplet of liquid. Proceed directly to Section 6: Setting the dose prescribed by your doctor.</td>
</tr>
</tbody>
</table>

If you do not see a tiny drop(s) of fluid at or near the tip the first time you use a new pen:

3. Gently turn the dose setting knob clockwise until it **reads 25** in the **Dose Feedback Window**. You can turn the dose knob backwards if you turn it past 25 (Fig. 5).

2. Hold the pen with the needle pointing upward.
3. Tap the reservoir holder gently (Fig. 6).
4. Press the dose setting knob **as far as it will go**. A tiny drop of liquid will appear at the tip of the needle (Fig. 7).
5. Verify that the **Dose Feedback Window** reads "0" (Fig. 8).
6. Proceed to **Section 6: Setting the dose prescribed by your doctor**.
6. Setting the dose prescribed by your doctor

6.1. Turn the dose setting knob until your intended dose shows in the Dose Feedback Window.

- Turn the dose setting knob forward to dial up according to the dose that was prescribed by your doctor.

- If needed, turn the dose setting knob backward to correct the dose.

**Warning:** Check that the Dose Feedback Window displays your complete prescribed dose before you move on to the next step.

7. Injecting the dose

7.1. Choose an injection site in the area your doctor or nurse has told you to use for the injection. To minimize skin irritation, select a different injection site each day.

7.2. Wipe the skin with an alcohol swab.

7.3. Verify once more that the Dose Feedback Window displays the correct dose.

7.4. Inject the dose as you were trained to do by your doctor or nurse.

- Slowly push the needle into the skin entirely (Fig. 9).

- **Slowly press the dose knob down as far as it will go** and hold it to complete the full injection.

- Hold the dose knob down for a minimum of 5 seconds to ensure you inject the full dose (Fig. 10).

- The dose number shown in the Dose Feedback Window will turn back to 0.

- After a minimum of 5 seconds, pull the needle out of the skin while keeping the dose setting knob pressed down (Fig. 11).

- When the needle is out of the skin, release the dose setting knob.

**Caution:** Do not release the dose knob until you remove the needle from the skin.
Warning: Always make sure to use a new needle for each injection.

8. After the injection

8.1. Verify you have given a complete injection.

- Check that the Dose Feedback Window shows “0”.

Warning: If the Dose Feedback Window shows a number higher than 0, the Pergoveris pre-filled pen is empty and you have not received your full prescribed dose.

8.2. Complete a partial injection (only when needed).

- The Dose Feedback Window will indicate the missing amount you need to inject using a new pen.

- Repeat Section 4 (Getting familiar with your Pergoveris pre-filled pen) through Section 5 (Getting your Pergoveris pre-filled pen ready for injection) with a second pen.

- Set the dose to the missing amount you recorded in the treatment diary OR the number still displayed in the Dose Feedback Window on your previous pen, and inject.

8.3. Removing the needle after each injection.

- Place the outer needle cap on a flat surface.
- Hold the Pergoveris pre-filled pen firmly with one hand, and slip the needle into the outer needle cap.
- Continue by pushing the capped needle against a firm surface until you hear a “click”.
- Grip the outer needle cap and unscrew the needle by turning anti-clockwise. Dispose of the used needle safely.
- Recap the pen.

Warning: Never reuse any used needle. Never share needles.

8.4. Storing the Pergoveris pre-filled pen.

Caution: Never store the pen with the needle still attached. Always remove the needle from the Pergoveris pre-filled pen before replacing the pen cap.

- Store the pen in its original packaging in a safe place and as indicated in the package leaflet.
- When the pen is empty, ask your pharmacist how to dispose of it.

**Warning:** Medicine should not be disposed of via wastewater or household waste.

### 9. Pergoveris pre-filled pen treatment diary

<table>
<thead>
<tr>
<th>Day Number</th>
<th>Date</th>
<th>Time</th>
<th>Pen Volume</th>
<th>Prescribed Dose</th>
<th>Amount Set to Inject</th>
<th>Amount to Be Set for a Second Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>/</td>
<td>:</td>
<td></td>
<td>1210.8 × 7.50 [SU100] 7.16</td>
<td></td>
<td>if &quot;O&quot;, injection complete</td>
<td>if not &quot;O&quot;, and second injection Inject this amount using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td></td>
<td>1210.8 × 7.50 [SU100] 7.16</td>
<td></td>
<td>if &quot;O&quot;, injection complete</td>
<td>if not &quot;O&quot;, and second injection Inject this amount using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td></td>
<td>1210.8 × 7.50 [SU100] 7.16</td>
<td></td>
<td>if &quot;O&quot;, injection complete</td>
<td>if not &quot;O&quot;, and second injection Inject this amount using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td></td>
<td>1210.8 × 7.50 [SU100] 7.16</td>
<td></td>
<td>if &quot;O&quot;, injection complete</td>
<td>if not &quot;O&quot;, and second injection Inject this amount using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td></td>
<td>1210.8 × 7.50 [SU100] 7.16</td>
<td></td>
<td>if &quot;O&quot;, injection complete</td>
<td>if not &quot;O&quot;, and second injection Inject this amount using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td></td>
<td>1210.8 × 7.50 [SU100] 7.16</td>
<td></td>
<td>if &quot;O&quot;, injection complete</td>
<td>if not &quot;O&quot;, and second injection Inject this amount using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td></td>
<td>1210.8 × 7.50 [SU100] 7.16</td>
<td></td>
<td>if &quot;O&quot;, injection complete</td>
<td>if not &quot;O&quot;, and second injection Inject this amount using new pen</td>
</tr>
<tr>
<td>/</td>
<td>:</td>
<td></td>
<td>1210.8 × 7.50 [SU100] 7.16</td>
<td></td>
<td>if &quot;O&quot;, injection complete</td>
<td>if not &quot;O&quot;, and second injection Inject this amount using new pen</td>
</tr>
</tbody>
</table>

This instructions for use was last revised in: