

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.

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 disorders.

Posology

In LH and FSH deficient women, the objective of Pergoveris therapy is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). Pergoveris should be given as a course of daily injections. If the patient is amenorrhoeic and has low endogenous oestrogen secretion, treatment can commence at any time.

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).

Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7 to 14 day intervals and preferably by 37.5 to 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 to 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 or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Special populations

Elderly

There is no relevant indication for the use of Pergoveris in the elderly population. Safety and efficacy 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

Traceability

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

General recommendations

Pergoveris contains potent gonadotropic 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.

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.

Gonadotropin 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.

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 gonadotropins, 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 gonadotropins may further increase the risk. In these women, the benefits of gonadotropin administration need to be weighed against the risks. It should be noted however, that pregnancy itself as well as OHSS also carries an increased risk of thromboembolic events.

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ 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

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

Pharmacodynamic effects

Inhibin and oestradiol levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while oestradiol levels take more time and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after about 4 to 5 days of r-hFSH daily dosing and, depending on patient response, the maximum effect is reached after about 10 days from the start of gonadotropin administration. The primary effect resulting from administration of r-hLH is a dose-related increase of E2 secretion, enhancing the effect of r-hFSH on follicular growth.

Clinical efficacy

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. In these trials the ovulation rate per cycle was 70 to 75%. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

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

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.

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% 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 9 to 11 hours. The steady state volume of distribution is in the range of 5 to 14 L. Lutropin alfa shows linear pharmacokinetics, as assessed by AUC which is directly proportional to the dose administered.

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

Elimination

Total clearance is in the range of 1.7 to 1.8 L/h, and less than 5% of the dose is excreted in the urine.

5.3 Preclinical safety data

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

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

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: 8 May 2017

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 to 7.5, its osmolality is 250 to 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.

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 disorders.

Posology

In LH and FSH deficient women, the objective of Pergoveris therapy is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). Pergoveris should be given as a course of daily injections. If the patient is amenorrhoeic and has low endogenous oestrogen secretion, treatment can commence at any time.

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).

Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7 to 14 day intervals and preferably by 37.5 to 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 to 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 or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Special populations

Elderly

There is no relevant indication for the use of Pergoveris in the elderly population. Safety and efficacy 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
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In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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Gonadotropin 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.

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 gonadotropins, 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 gonadotropins may further increase the risk. In these women, the benefits of gonadotropin administration need to be weighed against the risks. It should be noted however, that pregnancy itself as well as OHSS also carries an increased risk of thromboembolic events.

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ 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

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

Pharmacodynamic effects

Inhibin and oestradiol levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while oestradiol levels take more time and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after about 4 to 5 days of r-hFSH daily dosing and, depending on patient response, the maximum effect is reached after about 10 days from the start of gonadotropin administration. The primary effect resulting from administration of r-hLH is a dose-related increase of E2 secretion, enhancing the effect of r-hFSH on follicular growth.

Clinical efficacy

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. In these trials the ovulation rate per cycle was 70 to 75%. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

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

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.

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% 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 9 to 11 hours. The steady state volume of distribution is in the range of 5 to 14 L. Lutropin alfa shows linear pharmacokinetics, as assessed by AUC which is directly proportional to the dose administered.

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

Elimination

Total clearance is in the range of 1.7 to 1.8 L/h, and less than 5% of the dose is excreted in the urine.

5.3 Preclinical safety data

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

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

3 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 solution must be discarded not later than 28 days after first opening.

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 and the “Instructions for use”.

7. MARKETING AUTHORISATION HOLDER

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

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: 8 May 2017

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 (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 to 7.5, its osmolality is 250 to 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.

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 disorders.

Posology

In LH and FSH deficient women, the objective of Pergoveris therapy is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). Pergoveris should be given as a course of daily injections. If the patient is amenorrhoeic and has low endogenous oestrogen secretion, treatment can commence at any time.

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).

Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7 to 14 day intervals and preferably by 37.5 to 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 to 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 or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Special populations

Elderly

There is no relevant indication for the use of Pergoveris in the elderly population. Safety and efficacy 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

Traceability

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

General recommendations

Pergoveris contains potent gonadotropic 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.

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.

Gonadotropin 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.

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 gonadotropins, 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 gonadotropins may further increase the risk. In these women, the benefits of gonadotropin administration need to be weighed against the risks. It should be noted however, that pregnancy itself as well as OHSS also carries an increased risk of thromboembolic events.

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ 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

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

Pharmacodynamic effects

Inhibin and oestradiol levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while oestradiol levels take more time and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after about 4 to 5 days of r-hFSH daily dosing and, depending on patient response, the maximum effect is reached after about 10 days from the start of gonadotropin administration. The primary effect resulting from administration of r-hLH is a dose-related increase of E2 secretion, enhancing the effect of r-hFSH on follicular growth.

Clinical efficacy

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. In these trials the ovulation rate per cycle was 70 to 75%. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

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

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.

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% 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 9 to 11 hours. The steady state volume of distribution is in the range of 5 to 14 L. Lutropin alfa shows linear pharmacokinetics, as assessed by AUC which is directly proportional to the dose administered.

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

Elimination

Total clearance is in the range of 1.7 to 1.8 L/h, and less than 5% of the dose is excreted in the urine.

5.3 Preclinical safety data

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

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

3 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 solution must be discarded not later than 28 days after first opening.

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 and the “Instructions for use”.

7. MARKETING AUTHORISATION HOLDER

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

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: 8 May 2017

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 (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 to 7.5, its osmolality is 250 to 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.

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 disorders.

Posology

In LH and FSH deficient women, the objective of Pergoveris therapy is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). Pergoveris should be given as a course of daily injections. If the patient is amenorrhoeic and has low endogenous oestrogen secretion, treatment can commence at any time.

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).

Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7 to 14 day intervals and preferably by 37.5 to 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 to 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 or another medically assisted reproduction procedure may be performed based on the physician's judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Special populations

Elderly

There is no relevant indication for the use of Pergoveris in the elderly population. Safety and efficacy 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

Traceability

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

General recommendations

Pergoveris contains potent gonadotropic 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.

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.

Gonadotropin 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.

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 gonadotropins, 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 $> 5\,500\text{ pg/mL}$ or $> 20\,200\text{ pmol/L}$ 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 gonadotropins may further increase the risk. In these women, the benefits of gonadotropin administration need to be weighed against the risks. It should be noted however, that pregnancy itself as well as OHSS also carries an increased risk of thromboembolic events.

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ 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

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

Pharmacodynamic effects

Inhibin and oestradiol levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while oestradiol levels take more time and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after about 4 to 5 days of r-hFSH daily dosing and, depending on patient response, the maximum effect is reached after about 10 days from the start of gonadotropin administration. The primary effect resulting from administration of r-hLH is a dose-related increase of E2 secretion, enhancing the effect of r-hFSH on follicular growth.

Clinical efficacy

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. In these trials the ovulation rate per cycle was 70 to 75%. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

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

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.

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

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 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

Elimination

Total clearance is 0.6 L/h and about 12% 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 9 to 11 hours. The steady state volume of distribution is in the range of 5 to 14 L. Lutropin alfa shows linear pharmacokinetics, as assessed by AUC which is directly proportional to the dose administered.

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

Elimination

Total clearance is in the range of 1.7 to 1.8 L/h, and less than 5% of the dose is excreted in the urine.

5.3 Preclinical safety data

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

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

3 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 solution must be discarded not later than 28 days after first opening.

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 and the “Instructions for use”.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/07/396/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 June 2007
Date of latest renewal: 8 May 2017

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

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

Name and address of the manufacturers of the biological active substances

Merck Serono S.A.
Zone Industrielle de l'Ourietta
1170 Aubonne
Switzerland

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

Name and address of the manufacturer responsible for batch release

Merck Serono S.p.A.
Via delle Magnolie 15 (Zona Industriale)
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 (PSURs)**

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**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 AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/396/001 1 vial of powder for solution for injection.
1 vial of solvent.

EU/1/07/396/002 3 vials of powder for solution for injection.
3 vials of solvent.

EU/1/07/396/003 10 vials of powder for solution for injection.
10 vials of solvent.

13. BATCH NUMBER

Batch
Solvent Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

pergoveris 150 iu/75 iu

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|---|
| 17. UNIQUE IDENTIFIER – 2D BARCODE |
|---|

2D barcode carrying the unique identifier included.

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| 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA |
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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 |
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|--|
| 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION |
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Solvent for Pergoveris
water for injections

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|------------------------------------|
| 2. METHOD OF ADMINISTRATION |
|------------------------------------|

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|-----------------------|
| 3. EXPIRY DATE |
|-----------------------|

EXP

| |
|------------------------|
| 4. BATCH NUMBER |
|------------------------|

Batch

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

12. MARKETING AUTHORISATION 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 Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

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

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

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

Pergoveris (900 IU + 450 IU)/1.44 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

900 IU r-hFSH- 450 IU r-hLH/1.44 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, 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 gonadotropin, 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 that is to say essentially “sodium-free”.

3. How to use Pergoveris

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

Using this medicine

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

How much to use

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

- According to your response, your doctor may decide to add every day a dose of 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 or another medically assisted reproduction procedure may be performed based on your doctor's judgment.

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

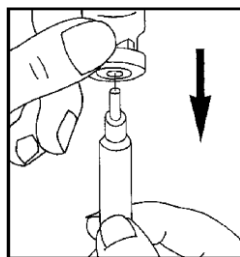
2. Get together everything you need and lay them out

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

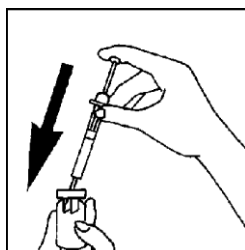
Not provided in the pack:

- 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

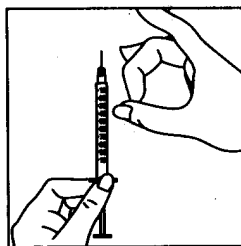


- Remove the protective cap from the vial filled with water (solvent vial).
- Attach the needle for preparation to the empty syringe for injection.
- Draw up some air into the syringe by pulling the plunger to approximately the 1 mL mark.
- Insert the needle into the vial, push the plunger to expel the 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.



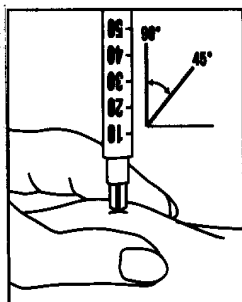
- Remove the protective cap from the vial filled with Pergoveris powder.
- Pick up your syringe and slowly inject the contents of the syringe into the vial of powder.
- Swirl gently without removing the syringe. Do not shake.
- After the powder has dissolved (which usually occurs immediately), check 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 Europe B.V., Gustav Mahlerplein 102, 1082 MA Amsterdam, The Netherlands

Manufacturer

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

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>.

Package leaflet: Information for the user

Pergoveris (300 IU + 150 IU)/0.48 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 gonadotropin, 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 that is to say 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 the “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 or another medically assisted reproduction procedure may be performed based on your doctor's judgment.

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 any medicine left in your pre-filled pen after 28 days.

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

Manufacturer

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

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>.

Instructions for Use

Pergoveris

(300 IU + 150 IU)/0.48 mL (450 IU + 225 IU)/0.72 mL (900 IU + 450 IU)/1.44 mL

Solution for injection in pre-filled pen
Follitropin alfa/Lutropin alfa

Important information about the Pergoveris pre-filled pen

- Read the Instructions for Use and the Package Leaflet before using your Pergoveris pre-filled pen.
- Always follow all directions in this Instructions for Use and training provided by your healthcare provider as they may differ from your past experience. This information will allow to prevent incorrect treatment or infection by needle stick or broken glass injury.
- 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.
- Your healthcare provider will tell you how many Pergoveris pre-filled pens you need to complete your treatment.
- Give yourself the injection at the same time each day.
- 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.

Note:

- The maximum dose you can dial is 300 IU for the (300 IU + 150 IU)/0.48 mL presentation.
- The maximum dose you can dial is 450 IU for both the (450 IU + 225 IU)/0.72 mL and the (900 IU + 450 IU)/1.44 mL presentations.
- The dose setting knob turns in increments of 12.5 IU to reach your intended dose.

Refer to the Package leaflet for more information on the recommended dose regimen and always follow the dose recommended by your healthcare provider.

- The numbers in the **Dose Feedback Window** represent the number of International Units, or IUs, and show the dose of follitropin alfa. Your healthcare provider 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 (Figure 1).

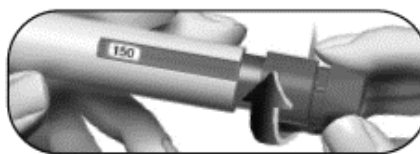


Fig. 1

- b. Verify a complete injection (Figure 2).



Fig. 2

- c. Read the dose remaining to be injected with a second pen (Figure 3).



Fig. 3

- Remove the needle from the pen immediately after each injection.

Do not reuse needles.

Do not share the pen and/or needles with another person.

Do not use the Pergoveris pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

How to use your Pergoveris pre-filled pen treatment diary


A treatment diary is included at the end of the Instructions for Use. Use the treatment diary to record the amount injected.

Injecting an incorrect amount of medicine could affect your treatment.

- 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).
- Check you dial 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).

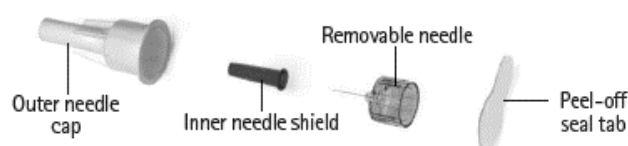
Using your treatment diary to record your daily injection(s) allows you to verify every day that you received the full prescribed dose.

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

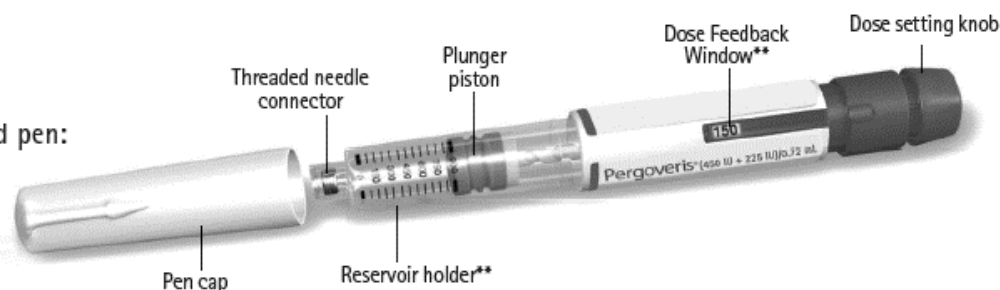
| 1 Treatment Day Number | 2 Date | 3 Time | 4 Pen Volume (300 IU + 150 IU)/0.48 mL (450 IU + 225 IU)/0.72 mL (900 IU + 450 IU)/1.44 mL | 5 Prescribed Dose | 8 Dose Feedback Window | | |
|---------------------------------|-----------|-----------|--|-------------------------|---------------------------|--|--|
| | | | | | Amount Set to Inject | Amount to Be Set for a Second Injection  | |
| #1 | 10/06 | 19:00 | 450 IU + 225 IU | 150 IU/75 IU | 150 | <input checked="" type="checkbox"/> if “0”, injection complete | <input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen |
| #2 | 11/06 | 19:00 | 450 IU + 225 IU | 150 IU/75 IU | 150 | <input checked="" type="checkbox"/> if “0”, injection complete | <input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen |
| #3 | 12/06 | 19:00 | 450 IU + 225 IU | 225 IU/112.5 IU | 225 | <input type="checkbox"/> if “0”, injection complete | <input checked="" type="checkbox"/> if not “0”, need second injection Inject this amount .75..using new pen |
| #3 | 12/06 | 19:00 | 450 IU + 225 IU | N/A | 75 | <input checked="" type="checkbox"/> if “0”, injection complete | <input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen |

Get familiar with your Pergoveris pre-filled pen

Your needle*:



Your pre-filled pen:



Pergoveris® (450 IU + 225 IU)/0.72 mL pen shown here.

* For illustration purposes only. The needles supplied may look slightly different.

** The numbers in the **Dose Feedback Window** and reservoir holder represent the number of International Units (IU) of medicine.

Step 1 Gather your supplies

- 1.1** Let the pre-filled pen sit at room temperature for at least 30 minutes before use to allow the medicine to reach room temperature.

Do not use a microwave or other heating element to warm up the pen.

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

- 1.3** You will also need (not included in the pack):

- Alcohol swabs and a sharps container (Figure 4)

- 1.4** Wash your hands with soap and water and dry them well (Figure 5).

- 1.5** Use your hand to remove the Pergoveris pre-filled pen from the pack.

Do not use any tools, using tools might damage the pen.

- 1.6** Check the name on the pre-filled pen says Pergoveris.

- 1.7** Check the expiration date on the pen label (Figure 6).

Do not use the Pergoveris pre-filled pen if the expiration date has passed or if your pre-filled pen does not say Pergoveris.



Fig. 4



Fig. 5

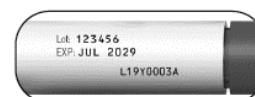


Fig. 6

Step 2 Get ready for injection

- 2.1 Pull-off the pen cap (Figure 7).
- 2.2 Check that medicine is clear, colourless and does not contain particles.
- Do not** use the pre-filled pen if the medicine is discolored or cloudy, as this can cause an infection.
- 2.3 Check that the Dose Feedback Window is set to “0” (Figure 8).

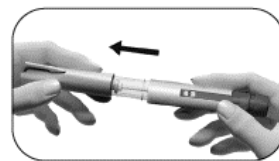


Fig. 7



Fig. 8

Choose your injection site:

- 2.4 Your healthcare provider should show you the injection sites to use around your stomach area (Figure 9). To minimize skin irritation, select a different injection site each day.
 - 2.5 Clean the skin at the injection site by wiping with an alcohol swab.
- Do not** touch or cover the cleaned skin.

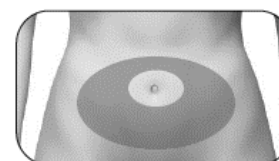


Fig. 9

Step 3 Attach your needle

Important: Always make sure to use a new needle for each injection.

Re-using needles can cause infections

- 3.1 Get a new needle. Only use the “single-use” needles supplied.
- 3.2 Check that the outer needle cap is not damaged.
- 3.3 Hold the outer needle cap firmly.
- 3.4 Check that the peel-off seal on the outer needle cap is not damaged or loose, and that expiration date has not passed (Figure 10).
- 3.5 Remove the peel-off seal (Figure 11).

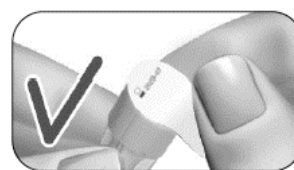


Fig. 10

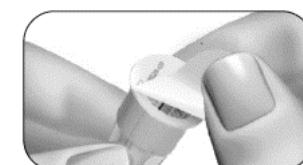


Fig. 11

Do not use the needle if it is damaged, expired or if the outer needle cap or the peel-off seal is damaged or loose. Using expired needles or needles with damaged peel-off seal or outer needle cap can lead to infection. Throw it away in a sharps container and get a new needle.

- 3.6 Screw the outer needle cap onto the threaded tip of the Pergoveris pre-filled pen until you feel a light resistance (Figure 12).



Fig. 12

Do not attach the needle too tightly; the needle could be difficult to remove after the injection.

- 3.7 Remove the outer needle cap by pulling it gently (Figure 13).

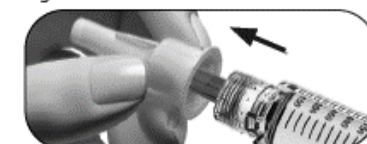


Fig. 13

- 3.8 Put it aside for later use (Figure 14).

Do not discard the outer needle cap, as it will prevent needle stick injury and infection when detaching the needle from the pre-filled pen.

- 3.9 Hold the Pergoveris pre-filled pen with the needle pointing upward (Figure 15).



Fig. 14



Fig. 15

Fig. 16

3.10 Carefully remove and discard the inner needle shield (Figure 16).

Do not recap the needle with the inner needle shield, as it can lead to needle stick injury and infection.

3.11 Look closely at the tip of the needle for tiny droplet(s) of liquid (Figure 17).

| If | Then |
|-----------------|--|
| Using a new pen | Check for a droplet of liquid at the tip of the needle. <ul style="list-style-type: none"> • If you see a tiny droplet, proceed to Step 4 Dial your dose. • If you do not see a tiny droplet at or near the needle tip, you must perform the steps in the following section to remove air in the system. |
| Reusing a pen | It is NOT required to check for a droplet of liquid. Proceed directly to Step 4 Dial your dose. |

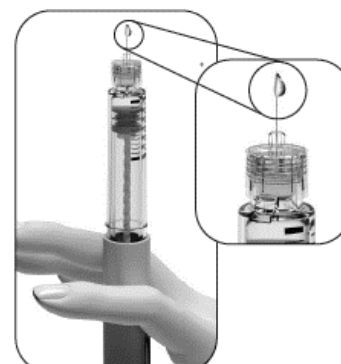


Fig. 17

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

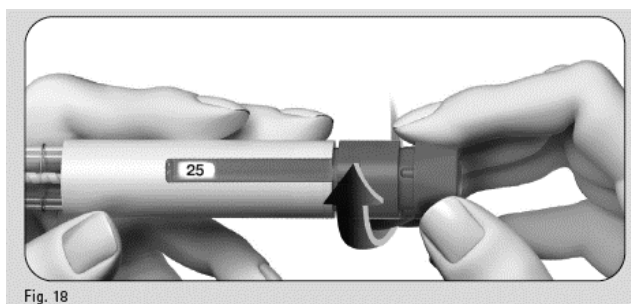


Fig. 18

1. Gently turn the dose setting knob forward until it reads “25” in the **Dose Feedback Window** (Figure 18).
 - You can turn the dose knob backward if you turn it past “25”.



Fig. 19

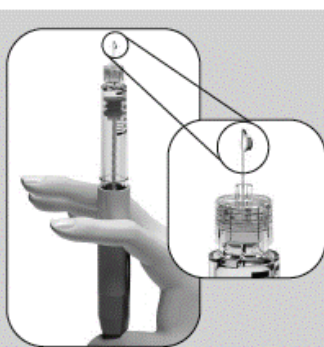


Fig. 20

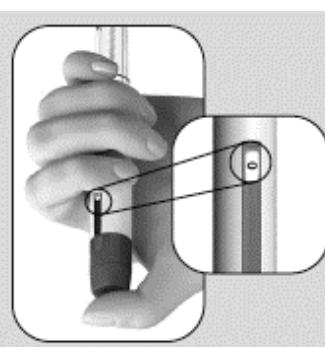


Fig. 21

2. Hold the pen with the needle pointing upward.
3. Tap the reservoir holder gently (Figure 19).
4. Press the dose setting knob **as far as it will go**. A tiny droplet of liquid will appear at the tip of the needle (Figure 20).
5. Check that the **Dose Feedback Window** reads “0” (Figure 21).
6. Proceed to **Step 4 Dial your dose.**

If a tiny droplet of liquid does not appear, contact your healthcare provider.

Step 4 Dial your dose

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

- Example: If your intended dose is “150” IU, confirm that the Dose Feedback Window reads “150” (Figure 22). Injecting an incorrect amount of medicine could affect your treatment.



Fig. 22

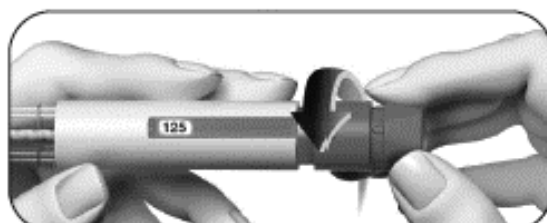


Fig. 23

- Turn the dose setting knob **forward** to dial up (Figure 22).
- You can turn the dose setting knob **backwards** if you turn it past your intended dose (Figure 23).

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

Step 5 Inject your dose

Important: Inject the dose as you were trained to do by your healthcare provider.

5.1 Slowly push the needle into the skin entirely (Figure 24).

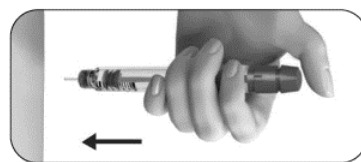


Fig. 24

5.2 Place your thumb in the middle of the dose setting knob. **Slowly press the dose knob down as far as it will go** and hold it to complete the full injection (Figure 25).

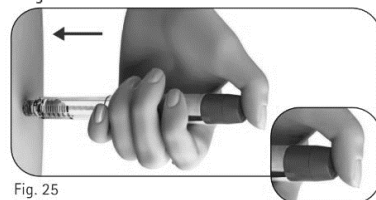


Fig. 25

Note: The larger the dose, the longer it will take to inject.

5.3 Hold the dose knob down for a minimum of 5 seconds before you remove the needle from your skin (Figure 26).

- 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** (Figure 27).
- When the needle is out of the skin, release the dose setting knob.

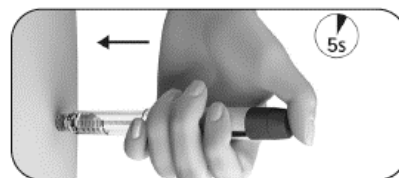


Fig. 26

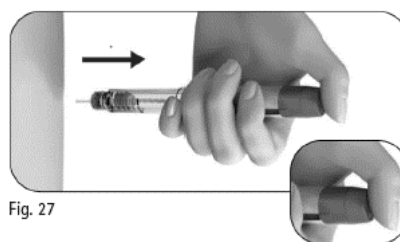


Fig. 27

Do not release the dose knob until you remove the needle from the skin.

Step 6 Remove the needle after each injection

6.1 Place the outer needle cap on a flat surface.

6.2 Hold the Pergoveris pre-filled pen firmly with one hand and slip the needle into the outer needle cap (Figure 28).

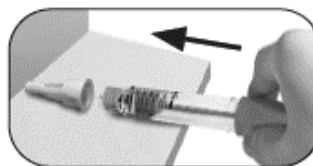


Fig. 28

6.3 Continue by pushing the capped needle against a firm surface until you hear a “click” (Figure 29).

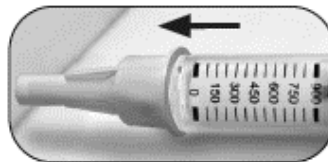


Fig. 29

6.4 Grip the outer needle cap and unscrew the needle by turning it in the opposite direction (Figure 30).

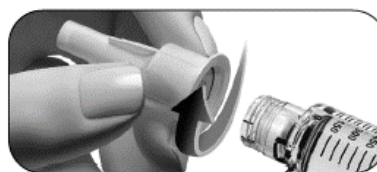


Fig. 30

6.5 Dispose of the used needle safely in a sharps container (Figure 31). Handle the needle with care to avoid getting injured by the needle.

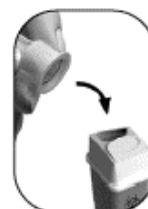


Fig. 31

Do not reuse or share any used needle.

Step 7 After the injection

7.1 Check you have given a complete injection

- Check that the Dose Feedback Window shows “0” (Figure 32).

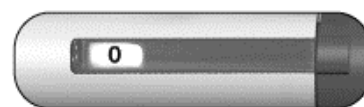


Fig. 32

If the Dose Feedback Window shows “0”, you have completed your dose.

If the Dose Feedback Window shows a number **higher than “0”**, the Pergoveris pre-filled pen is empty. You have not received your full prescribed dose and you must perform step 7.2 below.

7.2 Complete a partial injection (only when needed):

- The **Dose Feedback Window** will indicate the missing amount you need to inject using a new pen. In the example shown, the missing amount is “50” IU (Figure 33).
- To complete the dose with a second pen, repeat Steps 1 through 8.



Fig. 33

Step 8 Store the Pergoveris pre-filled pen

- 8.1** Put the pen cap back onto the pen to avoid infection (Figure 34).

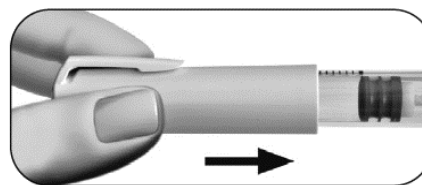


Fig. 34


- 8.2** Store the pen in its original packaging in a safe place and as indicated in the Package Leaflet.
- 8.3** When the pen is empty, ask your healthcare provider how to dispose of it.

Do not store the pen with the needle still attached, as this may cause infection.

Do not reuse the Pergoveris pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

Contact your healthcare provider if you have questions.

Pergoveris pre-filled pen treatment diary

| 1 Treatment Day Number | 2 Date | 3 Time | 4 Pen Volume (300 IU + 150 IU)/0.48 mL (450 IU + 225 IU)/0.72 mL (900 IU + 450 IU)/1.44 mL | 5 Prescribed Dose | 6 7 8 Dose Feedback Window | | |
|---------------------------------|-----------|-----------|--|-------------------------|-------------------------------|---|---|
| | | | | | Amount Set to Inject | Amount to Be Set for a Second Injection  | |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen - |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
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| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |

This Instructions for Use has been 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 gonadotropin, 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 that is to say 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 the “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 or another medically assisted reproduction procedure may be performed based on your doctor's judgment.

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 any medicine left in your pre-filled pen after 28 days.

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

Manufacturer

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

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>.

Instructions for Use

Pergoveris

(300 IU + 150 IU)/0.48 mL (450 IU + 225 IU)/0.72 mL (900 IU + 450 IU)/1.44 mL

Solution for injection in pre-filled pen
Follitropin alfa/Lutropin alfa

Important information about the Pergoveris pre-filled pen

- Read the Instructions for Use and the Package Leaflet before using your Pergoveris pre-filled pen.
- Always follow all directions in this Instructions for Use and training provided by your healthcare provider as they may differ from your past experience. This information will allow to prevent incorrect treatment or infection by needle stick or broken glass injury.
- 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.
- Your healthcare provider will tell you how many Pergoveris pre-filled pens you need to complete your treatment.
- Give yourself the injection at the same time each day.
- The pen comes in 3 different multi-dose presentations:

(300 IU + 150 IU)/0.48 mL

(450 IU + 225 IU)/0.72 mL

900 IU + 450 IU)/1.44 mL

- Contains 0.48 mL of Pergoveris solution
- Contains 300 IU follitropin alfa and 150 IU lutropin alfa.
- Contains 0.72 mL of Pergoveris solution
- Contains 450 IU follitropin alfa and 225 IU lutropin alfa.
- Contains 1.44 mL of Pergoveris solution
- Contains 900 IU follitropin alfa and 450 IU lutropin alfa.

Note:

- The maximum dose you can dial is 300 IU for the (300 IU + 150 IU)/0.48 mL presentation.
- The maximum dose you can dial is 450 IU for both the (450 IU + 225 IU)/0.72 mL and the (900 IU + 450 IU)/1.44 mL presentations.
- The dose setting knob turns in increments of 12.5 IU to reach your intended dose.

Refer to the Package leaflet for more information on the recommended dose regimen and always follow the dose recommended by your healthcare provider.

- The numbers in the **Dose Feedback Window** represent the number of International Units, or IUs, and show the dose of follitropin alfa. Your healthcare provider 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 (Figure 1).

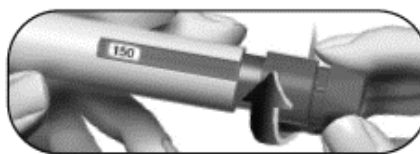


Fig. 1

- b. Verify a complete injection (Figure 2).



Fig. 2

- c. Read the dose remaining to be injected with a second pen (Figure 3).



Fig. 3

- Remove the needle from the pen immediately after each injection.

Do not reuse needles.

Do not share the pen and/or needles with another person.

Do not use the Pergoveris pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

How to use your Pergoveris pre-filled pen treatment diary


A treatment diary is included at the end of the Instructions for Use. Use the treatment diary to record the amount injected.

Injecting an incorrect amount of medicine could affect your treatment.

- 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).
- Check you dial 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).

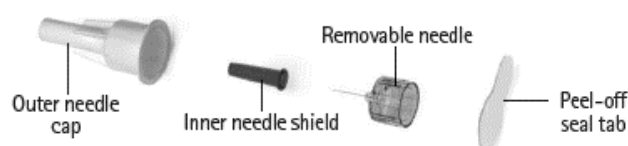
Using your treatment diary to record your daily injection(s) allows you to verify every day that you received the full prescribed dose.

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

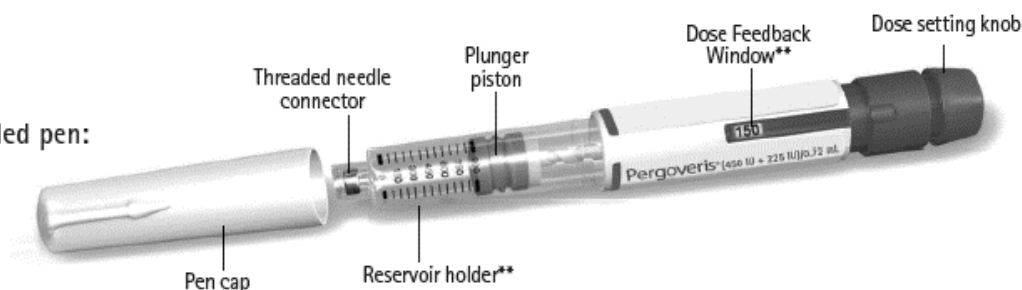
| 1 Treatment Day Number | 2 Date | 3 Time | 4 Pen Volume (300 IU + 150 IU)/0.48 mL (450 IU + 225 IU)/0.72 mL (900 IU + 450 IU)/1.44 mL | 5 Prescribed Dose | 6 7 8 Dose Feedback Window | | |
|---------------------------------|-----------|-----------|--|-------------------------|-------------------------------|--|--|
| | | | | | Amount Set to Inject | Amount to Be Set for a Second Injection  | |
| #1 | 10/06 | 19:00 | 450 IU + 225 IU | 150 IU/75 IU | 150 | <input checked="" type="checkbox"/> if “0”, injection complete | <input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen |
| #2 | 11/06 | 19:00 | 450 IU + 225 IU | 150 IU/75 IU | 150 | <input checked="" type="checkbox"/> if “0”, injection complete | <input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen |
| #3 | 12/06 | 19:00 | 450 IU + 225 IU | 225 IU/112.5 IU | 225 | <input type="checkbox"/> if “0”, injection complete | <input checked="" type="checkbox"/> if not “0”, need second injection Inject this amount .75..using new pen |
| #3 | 12/06 | 19:00 | 450 IU + 225 IU | N/A | 75 | <input checked="" type="checkbox"/> if “0”, injection complete | <input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen |

Get familiar with your Pergoveris pre-filled pen

Your needle*:



Your pre-filled pen:



Pergoveris® (450 IU + 225 IU)/0.72 mL pen shown here.

* For illustration purposes only. The needles supplied may look slightly different.

** The numbers in the **Dose Feedback Window** and reservoir holder represent the number of International Units (IU) of medicine.

Step 1 Gather your supplies

- 1.1** Let the pre-filled pen sit at room temperature for at least 30 minutes before use to allow the medicine to reach room temperature.

Do not use a microwave or other heating element to warm up the pen.

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

- 1.3** You will also need (not included in the pack):

- Alcohol swabs and a sharps container (Figure 4)

- 1.4** Wash your hands with soap and water and dry them well (Figure 5).

- 1.5** Use your hand to remove the Pergoveris pre-filled pen from the pack.

Do not use any tools, using tools might damage the pen.

- 1.6** Check the name on the pre-filled pen says Pergoveris.

- 1.7** Check the expiration date on the pen label (Figure 6).

Do not use the Pergoveris pre-filled pen if the expiration date has passed or if your pre-filled pen does not say Pergoveris.



Fig. 4

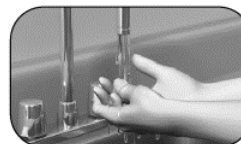


Fig. 5



Fig. 6

Step 2 Get ready for injection

- 2.1 Pull-off the pen cap (Figure 7).
- 2.2 Check that medicine is clear, colourless and does not contain particles.

Do not use the pre-filled pen if the medicine is discolored or cloudy, as this can cause an infection.

- 2.3 Check that the Dose Feedback Window is set to “0” (Figure 8).

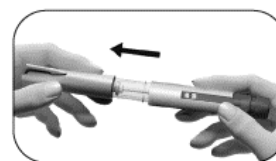


Fig. 7



Fig. 8

Choose your injection site:

- 2.4 Your healthcare provider should show you the injection sites to use around your stomach area (Figure 9). To minimize skin irritation, select a different injection site each day.
- 2.5 Clean the skin at the injection site by wiping with an alcohol swab.

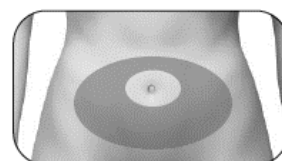


Fig. 9

Do not touch or cover the cleaned skin.

Step 3 Attach your needle

Important: Always make sure to use a new needle for each injection.

Re-using needles can cause infections

- 3.1 Get a new needle. Only use the “single-use” needles supplied.
- 3.2 Check that the outer needle cap is not damaged.
- 3.3 Hold the outer needle cap firmly.
- 3.4 Check that the peel-off seal on the outer needle cap is not damaged or loose, and that expiration date has not passed (Figure 10).
- 3.5 Remove the peel-off seal (Figure 11).

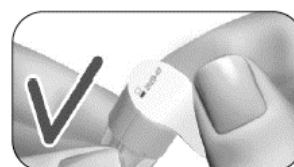


Fig. 10

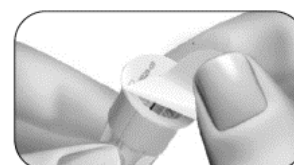


Fig. 11

Do not use the needle if it is damaged, expired or if the outer needle cap or the peel-off seal is damaged or loose. Using expired needles or needles with damaged peel-off seal or outer needle cap can lead to infection. Throw it away in a sharps container and get a new needle.

- 3.6 Screw the outer needle cap onto the threaded tip of the Pergoveris pre-filled pen until you feel a light resistance (Figure 12).



Fig. 12

Do not attach the needle too tightly; the needle could be difficult to remove after the injection.

- 3.7 Remove the outer needle cap by pulling it gently (Figure 13).

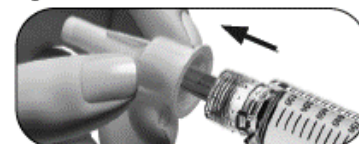


Fig. 13

- 3.8 Put it aside for later use (Figure 14).

Do not discard the outer needle cap, as it will prevent needle stick injury and infection when detaching the needle from the pre-filled pen.

- 3.9 Hold the Pergoveris pre-filled pen with the needle pointing upward (Figure 15).



Fig. 14



Fig. 15



Fig. 16

3.10 Carefully remove and discard the inner needle shield (Figure 16).

Do not recap the needle with the inner needle shield, as it can lead to needle stick injury and infection.

3.11 Look closely at the tip of the needle for tiny droplet(s) of liquid (Figure 17).

| If | Then |
|-----------------|--|
| Using a new pen | Check for a droplet of liquid at the tip of the needle. <ul style="list-style-type: none"> • If you see a tiny droplet, proceed to Step 4 Dial your dose. • If you do not see a tiny droplet at or near the needle tip, you must perform the steps in the following section to remove air in the system. |
| Reusing a pen | It is NOT required to check for a droplet of liquid. Proceed directly to Step 4 Dial your dose. |

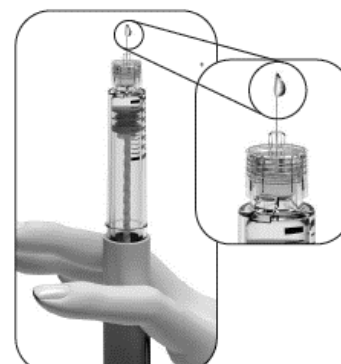


Fig. 17

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

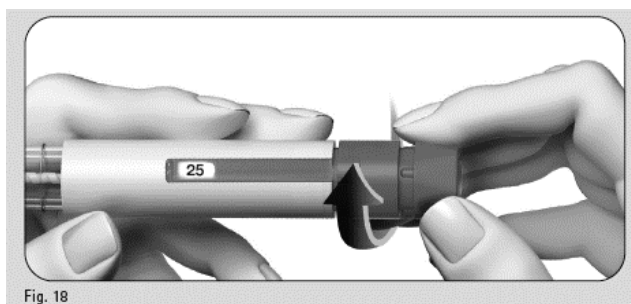


Fig. 18

1. Gently turn the dose setting knob forward until it reads “25” in the **Dose Feedback Window** (Figure 18).
 - You can turn the dose knob backward if you turn it past “25”.



Fig. 19

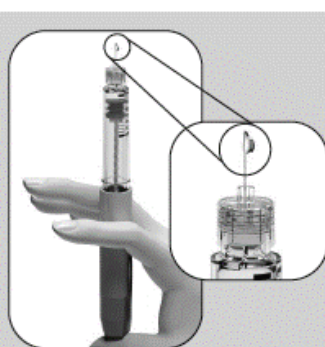


Fig. 20

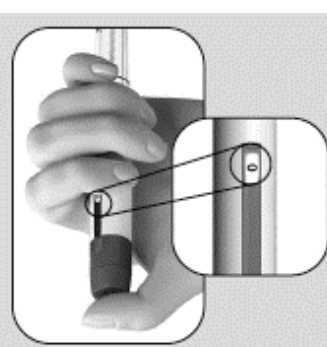


Fig. 21

2. Hold the pen with the needle pointing upward.
3. Tap the reservoir holder gently (Figure 19).
4. Press the dose setting knob **as far as it will go**. A tiny droplet of liquid will appear at the tip of the needle (Figure 20).
5. Check that the **Dose Feedback Window** reads “0” (Figure 21).
6. Proceed to **Step 4 Dial your dose.**

If a tiny droplet of liquid does not appear, contact your healthcare provider.

Step 4 Dial your dose

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

- Example: If your intended dose is “150 IU”, confirm that the Dose Feedback Window reads “150” (Figure 22). Injecting an incorrect amount of medicine could affect your treatment.



Fig. 22

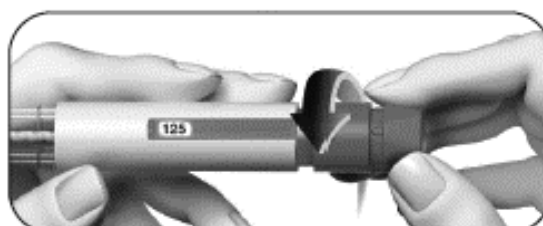


Fig. 23

- Turn the dose setting knob **forward** to dial up (Figure 22).
- You can turn the dose setting knob **backwards** if you turn it past your intended dose (Figure 23).

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

Step 5 Inject your dose

Important: Inject the dose as you were trained to do by your healthcare provider.

5.1 Slowly push the needle into the skin entirely (Figure 24).

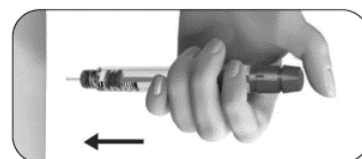


Fig. 24

5.2 Place your thumb in the middle of the dose setting knob. **Slowly press the dose knob down as far as it will go** and hold it to complete the full injection (Figure 25).

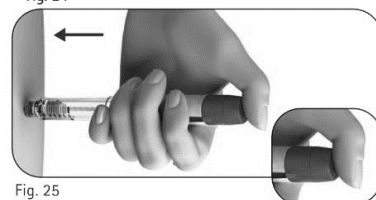


Fig. 25

Note: The larger the dose, the longer it will take to inject.

5.3 Hold the dose knob down for a minimum of 5 seconds before you remove the needle from your skin (Figure 26).

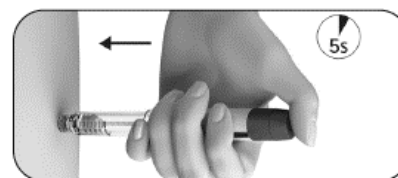


Fig. 26

- 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** (Figure 27).
 - When the needle is out of the skin, release the dose setting knob.

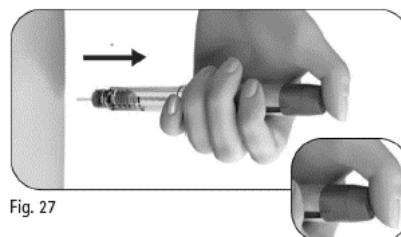


Fig. 27

Do not release the dose knob until you remove the needle from the skin.

Step 6 Remove the needle after each injection

- 6.1 Place the outer needle cap on a flat surface.
- 6.2 Hold the Pergoveris pre-filled pen firmly with one hand and slip the needle into the outer needle cap (Figure 28).
- 6.3 Continue by pushing the capped needle against a firm surface until you hear a “click” (Figure 29).
- 6.4 Grip the outer needle cap and unscrew the needle by turning it in the opposite direction (Figure 30).
- 6.5 Dispose of the used needle safely in a sharps container (Figure 31). Handle the needle with care to avoid getting injured by the needle.

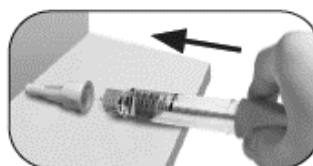


Fig. 28

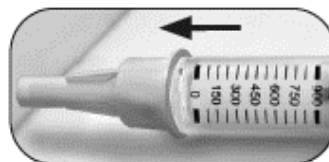


Fig. 29

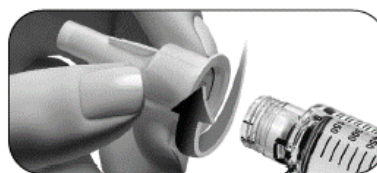


Fig. 30

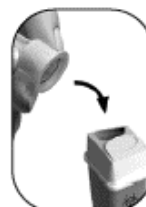


Fig. 31

Do not reuse or share any used needle.

Step 7 After the injection

- 7.1 Check you have given a complete injection
 - Check that the Dose Feedback Window shows “0” (Figure 32).

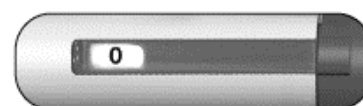


Fig. 32

If the Dose Feedback Window shows “0”, you have completed your dose.

If the Dose Feedback Window shows a number **higher than “0”**, the Pergoveris pre-filled pen is empty. You have not received your full prescribed dose and you must perform step 7.2 below.

- 7.2 Complete a partial injection (only when needed):
 - The **Dose Feedback Window** will indicate the missing amount you need to inject using a new pen. In the example shown, the missing amount is “50” IU (Figure 33).
 - To complete the dose with a second pen, repeat Steps 1 through 8.



Fig. 33

Step 8 Store the Pergoveris pre-filled pen

- 8.1** Put the pen cap back onto the pen to avoid infection (Figure 34).

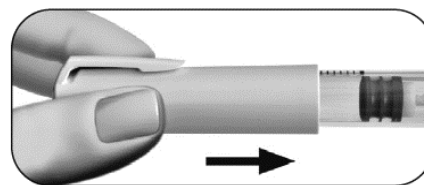


Fig. 34


- 8.2** Store the pen in its original packaging in a safe place and as indicated in the Package Leaflet.
- 8.3** When the pen is empty, ask your healthcare provider how to dispose of it.

Do not store the pen with the needle still attached, as this may cause infection.

Do not reuse the Pergoveris pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

Contact your healthcare provider if you have questions.

Pergoveris pre-filled pen treatment diary

| 1 Treatment Day Number | 2 Date | 3 Time | 4 Pen Volume (300 IU + 150 IU)/0.48 mL, (450 IU + 225 IU)/0.72 mL, (900 IU + 450 IU)/1.44 mL | 5 Prescribed Dose | 6 7 8 | | |
|---------------------------------|-----------|-----------|--|-------------------------|-------------------------|--|---|
| | | | | | Dose Feedback Window | | |
| | | | | | Amount Set to Inject | Amount to Be Set for a Second Injection  | |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen - |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |

This Instructions for Use has been last revised in:

Package leaflet: Information for the user

Pergoveris (900 IU + 450 IU)/1.44 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 gonadotropin, 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 that is to say 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 the “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 or another medically assisted reproduction procedure may be performed based on your doctor's judgment.

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 any medicine left in your pre-filled pen after 28 days.

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

Manufacturer

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

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>.

Instructions for Use

Pergoveris

(300 IU + 150 IU)/0.48 mL (450 IU + 225 IU)/0.72 mL (900 IU + 450 IU)/1.44 mL

Solution for injection in pre-filled pen
Follitropin alfa/Lutropin alfa

Important information about the Pergoveris pre-filled pen

- Read the Instructions for Use and the Package Leaflet before using your Pergoveris pre-filled pen.
- Always follow all directions in this Instructions for Use and training provided by your healthcare provider as they may differ from your past experience. This information will allow to prevent incorrect treatment or infection by needle stick or broken glass injury.
- 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.
- Your healthcare provider will tell you how many Pergoveris pre-filled pens you need to complete your treatment.
- Give yourself the injection at the same time each day.
- The pen comes in 3 different multi-dose presentations:

(300 IU + 150 IU)/0.48 mL

(450 IU + 225 IU)/0.72 mL

900 IU + 450 IU)/1.44 mL

- Contains 0.48 mL of Pergoveris solution
- Contains 300 IU follitropin alfa and 150 IU lutropin alfa.
- Contains 0.72 mL of Pergoveris solution
- Contains 450 IU follitropin alfa and 225 IU lutropin alfa.
- Contains 1.44 mL of Pergoveris solution
- Contains 900 IU follitropin alfa and 450 IU lutropin alfa.

Note:

- The maximum dose you can dial is 300 IU for the (300 IU + 150 IU)/0.48 mL presentation.
- The maximum dose you can dial is 450 IU for both the (450 IU + 225 IU)/0.72 mL and the (900 IU + 450 IU)/1.44 mL presentations.
- The dose setting knob turns in increments of 12.5 IU to reach your intended dose.

Refer to the Package leaflet for more information on the recommended dose regimen and always follow the dose recommended by your healthcare provider.

- The numbers in the **Dose Feedback Window** represent the number of International Units, or IUs, and show the dose of follitropin alfa. Your healthcare provider 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 (Figure 1).

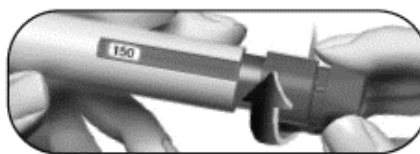


Fig. 1

- b. Verify a complete injection (Figure 2).



Fig. 2

- c. Read the dose remaining to be injected with a second pen (Figure 3).



Fig. 3

- Remove the needle from the pen immediately after each injection.

Do not reuse needles.

Do not share the pen and/or needles with another person.

Do not use the Pergoveris pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

How to use your Pergoveris pre-filled pen treatment diary


A treatment diary is included at the end of the Instructions for Use. Use the treatment diary to record the amount injected.

Injecting an incorrect amount of medicine could affect your treatment.

- 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).
- Check you dial 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).

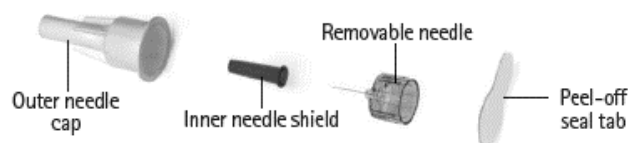
Using your treatment diary to record your daily injection(s) allows you to verify every day that you received the full prescribed dose.

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

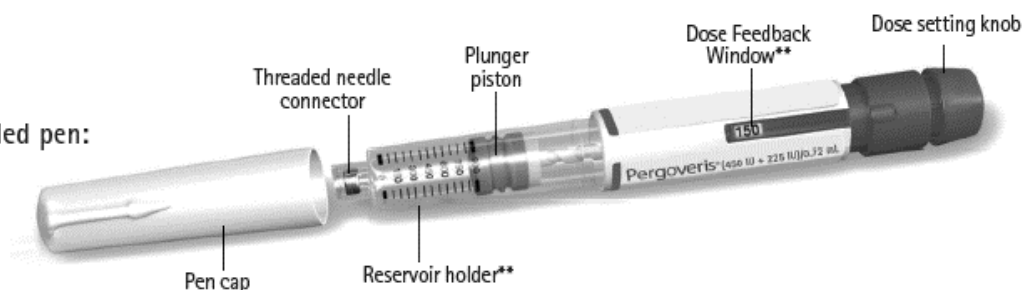
| 1 Treatment Day Number | 2 Date | 3 Time | 4 Pen Volume (300 IU + 150 IU)/0.48 mL (450 IU + 225 IU)/0.72 mL (900 IU + 450 IU)/1.44 mL | 5 Prescribed Dose | 8 Dose Feedback Window | | |
|---------------------------------|-----------|-----------|--|-------------------------|------------------------------|---|--|
| | | | | | 6 Amount Set to Inject | 7 Amount to Be Set for a Second Injection  | |
| #1 | 10/06 | 19:00 | 450 IU + 225 IU | 150 IU/75 IU | 150 | <input checked="" type="checkbox"/> if “0”, injection complete | <input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen |
| #2 | 11/06 | 19:00 | 450 IU + 225 IU | 150 IU/75 IU | 150 | <input checked="" type="checkbox"/> if “0”, injection complete | <input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen |
| #3 | 12/06 | 19:00 | 450 IU + 225 IU | 225 IU/112.5 IU | 225 | <input type="checkbox"/> if “0”, injection complete | <input checked="" type="checkbox"/> if not “0”, need second injection Inject this amount .75..using new pen |
| #3 | 12/06 | 19:00 | 450 IU + 225 IU | N/A | 75 | <input checked="" type="checkbox"/> if “0”, injection complete | <input type="checkbox"/> if not “0”, need second injection Inject this amountusing new pen |

Get familiar with your Pergoveris pre-filled pen

Your needle*:



Your pre-filled pen:



Pergoveris® (450 IU + 225 IU)/0.72 mL pen shown here.

* For illustration purposes only. The needles supplied may look slightly different.

** The numbers in the **Dose Feedback Window** and reservoir holder represent the number of International Units (IU) of medicine.

Step 1 Gather your supplies

- 1.1** Let the pre-filled pen sit at room temperature for at least 30 minutes before use to allow the medicine to reach room temperature.

Do not use a microwave or other heating element to warm up the pen.

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

- 1.3** You will also need (not included in the pack):

- Alcohol swabs and a sharps container (Figure 4)

- 1.4** Wash your hands with soap and water and dry them well (Figure 5).

- 1.5** Use your hand to remove the Pergoveris pre-filled pen from the pack.

Do not use any tools, using tools might damage the pen.

- 1.6** Check the name on the pre-filled pen says Pergoveris.

- 1.7** Check the **expiration date** on the pen label (Figure 6).

Do not use the Pergoveris pre-filled pen if the expiration date has passed or if your pre-filled pen does not say Pergoveris.

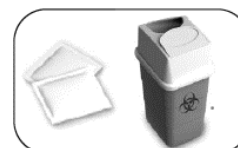


Fig. 4



Fig. 5

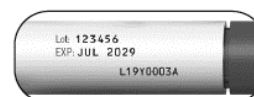


Fig. 6

Step 2 Get ready for injection

- 2.1 Pull-off the pen cap (Figure 7).
- 2.2 Check that medicine is clear, colourless and does not contain particles.

Do not use the pre-filled pen if the medicine is discolored or cloudy, as this can cause an infection.

- 2.3 Check that the Dose Feedback Window is set to “0” (Figure 8).

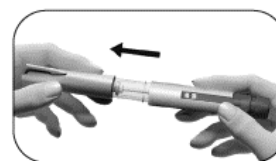


Fig. 7



Fig. 8

Choose your injection site:

- 2.4 Your healthcare provider should show you the injection sites to use around your stomach area (Figure 9). To minimize skin irritation, select a different injection site each day.
- 2.5 Clean the skin at the injection site by wiping with an alcohol swab.

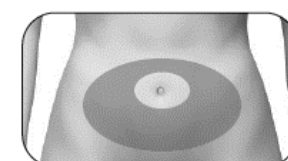


Fig. 9

Do not touch or cover the cleaned skin.

Step 3 Attach your needle

Important: Always make sure to use a new needle for each injection.

Re-using needles can cause infections

- 3.1 Get a new needle. Only use the “single-use” needles supplied.
- 3.2 Check that the outer needle cap is not damaged.
- 3.3 Hold the outer needle cap firmly.
- 3.4 Check that the peel-off seal on the outer needle cap is not damaged or loose, and that expiration date has not passed (Figure 10).
- 3.5 Remove the peel-off seal (Figure 11).

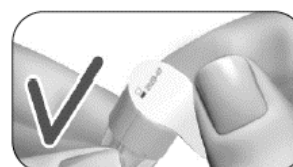


Fig. 10

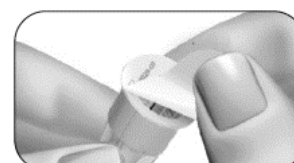


Fig. 11

Do not use the needle if it is damaged, expired or if the outer needle cap or the peel-off seal is damaged or loose. Using expired needles or needles with damaged peel-off seal or outer needle cap can lead to infection. Throw it away in a sharps container and get a new needle.



Fig. 12

- 3.6 Screw the outer needle cap onto the threaded tip of the Pergoveris pre-filled pen until you feel a light resistance (Figure 12).

Do not attach the needle too tightly; the needle could be difficult to remove after the injection.

- 3.7 Remove the outer needle cap by pulling it gently (Figure 13).



Fig. 13

- 3.8 Put it aside for later use (Figure 14).

Do not discard the outer needle cap, as it will prevent needle stick injury and infection when detaching the needle from the pre-filled pen.

- 3.9 Hold the Pergoveris pre-filled pen with the needle pointing upward (Figure 15).



Fig. 14

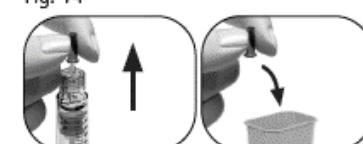


Fig. 15



Fig. 16

3.10 Carefully remove and discard the inner needle shield (Figure 16).

Do not recap the needle with the inner needle shield, as it can lead to needle stick injury and infection.

3.11 Look closely at the tip of the needle for tiny droplet(s) of liquid (Figure 17).

| If | Then |
|-----------------|--|
| Using a new pen | Check for a droplet of liquid at the tip of the needle. <ul style="list-style-type: none"> If you see a tiny droplet, proceed to Step 4 Dial your dose. If you do not see a tiny droplet at or near the needle tip, you must perform the steps in the following section to remove air in the system. |
| Reusing a pen | It is NOT required to check for a droplet of liquid. Proceed directly to Step 4 Dial your dose. |

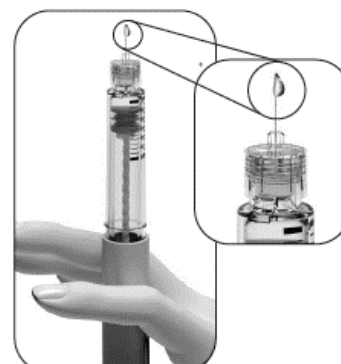


Fig. 17

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

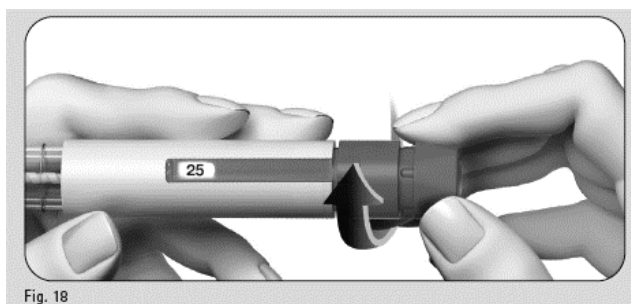


Fig. 18

1. Gently turn the dose setting knob forward until it reads “25” in the **Dose Feedback Window** (Figure 18).
 - You can turn the dose knob backward if you turn it past “25”.



Fig. 19

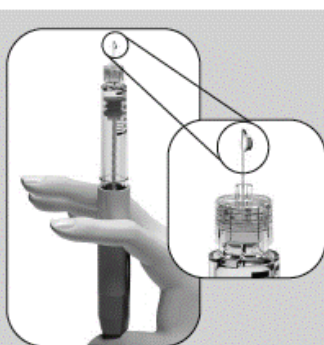


Fig. 20

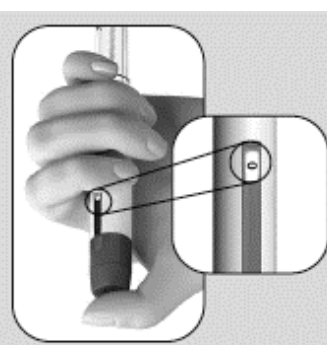


Fig. 21

2. Hold the pen with the needle pointing upward.
3. Tap the reservoir holder gently (Figure 19).
4. Press the dose setting knob **as far as it will go**. A tiny droplet of liquid will appear at the tip of the needle (Figure 20).
5. Check that the **Dose Feedback Window** reads “0” (Figure 21).
6. Proceed to **Step 4 Dial your dose.**

If a tiny droplet of liquid does not appear, contact your healthcare provider.

Step 4 Dial your dose

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

- Example: If your intended dose is “150 IU”, confirm that the Dose Feedback Window reads “150” (Figure 22). Injecting an incorrect amount of medicine could affect your treatment.

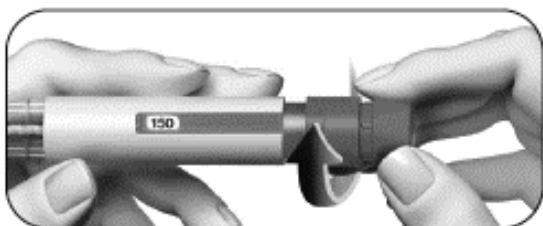


Fig. 22

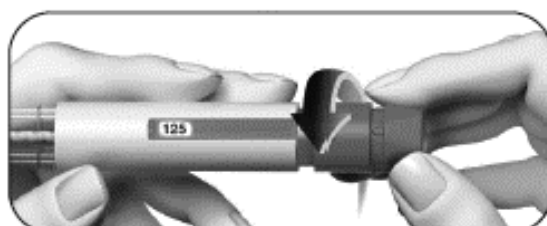


Fig. 23

- Turn the dose setting knob **forward** to dial up (Figure 22).
- You can turn the dose setting knob **backwards** if you turn it past your intended dose (Figure 23).

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

Step 5 Inject your dose

Important: Inject the dose as you were trained to do by your healthcare provider.

5.1 Slowly push the needle into the skin entirely (Figure 24).

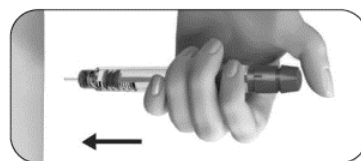


Fig. 24

5.2 Place your thumb in the middle of the dose setting knob.

Slowly press the dose knob down as far as it will go and hold it to complete the full injection (Figure 25).

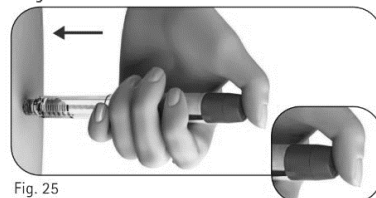


Fig. 25

Note: The larger the dose, the longer it will take to inject.

5.3 Hold the dose knob down for a minimum of 5 seconds before you remove the needle from your skin (Figure 26).

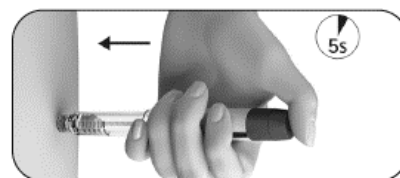


Fig. 26

- 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** (Figure 27).
- When the needle is out of the skin, release the dose setting knob.

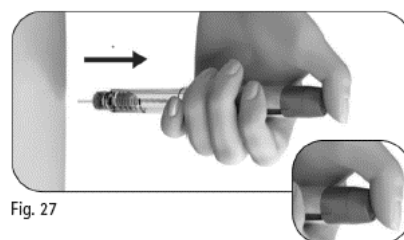


Fig. 27

Do not release the dose knob until you remove the needle from the skin.

Step 6 Remove the needle after each injection

6.1 Place the outer needle cap on a flat surface.

6.2 Hold the Pergoveris pre-filled pen firmly with one hand and slip the needle into the outer needle cap (Figure 28).

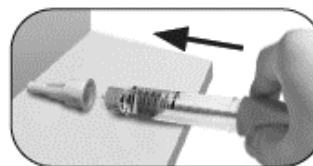


Fig. 28

6.3 Continue by pushing the capped needle against a firm surface until you hear a “click” (Figure 29).

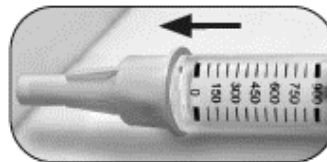


Fig. 29

6.4 Grip the outer needle cap and unscrew the needle by turning it in the opposite direction (Figure 30).

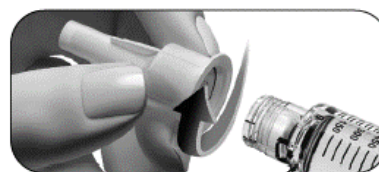


Fig. 30

6.5 Dispose of the used needle safely in a sharps container (Figure 31). Handle the needle with care to avoid getting injured by the needle.

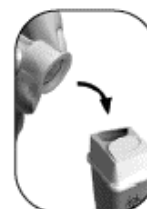


Fig. 31

Do not reuse or share any used needle.

Step 7 After the injection

7.1 Check you have given a complete injection

- Check that the Dose Feedback Window shows “0” (Figure 32).

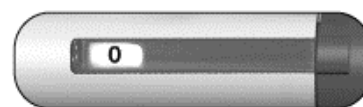


Fig. 32

If the Dose Feedback Window shows “0”, you have completed your dose.

If the Dose Feedback Window shows a number **higher than “0”**, the Pergoveris pre-filled pen is empty. You have not received your full prescribed dose and you must perform step 7.2 below.

7.2 Complete a partial injection (only when needed):

- The **Dose Feedback Window** will indicate the missing amount you need to inject using a new pen. In the example shown, the missing amount is “50” IU (Figure 33).
- To complete the dose with a second pen, repeat Steps 1 through 8.



Fig. 33

Step 8 Store the Pergoveris pre-filled pen

- 8.1** Put the pen cap back onto the pen to avoid infection (Figure 34).

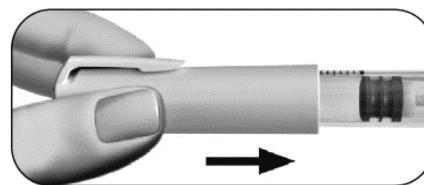


Fig. 34


- 8.2** Store the pen in its original packaging in a safe place and as indicated in the Package Leaflet.
- 8.3** When the pen is empty, ask your healthcare provider how to dispose of it.

Do not store the pen with the needle still attached, as this may cause infection.

Do not reuse the Pergoveris pre-filled pen if it has been dropped, or the pen is cracked or damaged as this can cause injury.

Contact your healthcare provider if you have questions.

Pergoveris pre-filled pen treatment diary

| 1 Treatment Day Number | 2 Date | 3 Time | 4 Pen Volume (300 IU + 150 IU)/0.48 mL (450 IU + 225 IU)/0.72 mL (900 IU + 450 IU)/1.44 mL | 5 Prescribed Dose | 6 7 8 Dose Feedback Window | | |
|---------------------------------|-----------|-----------|--|-------------------------|-------------------------------|---|---|
| | | | | | Amount Set to Inject | Amount to Be Set for a Second Injection  | |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen - |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |
| | / | : | | | | <input type="checkbox"/> if "0", injection complete | <input type="checkbox"/> if not "0", need second injection Inject this amountusing new pen |

This Instructions for Use has been last revised in: