

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 women with severe LH and FSH deficiency.

In clinical trials, these patients were defined by an endogenous serum LH level < 1.2 IU/L.

4.2 Posology and method of administration

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

Posology

In LH and FSH deficient women (hypogonadotrophic hypogonadism), the objective of Pergoveris therapy is to develop a single mature Graafian follicle from which the oocyte will be liberated after the administration of human chorionic gonadotrophin (hCG). Pergoveris should be given as a course of daily injections. Since these patients are

amenorrhoeic and have low endogenous oestrogen secretion, treatment can commence at any time.

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

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7-14 day intervals and preferably by 37.5-75 IU increments using a licensed follitropin alfa preparation. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.

When an optimal response is obtained, a single injection of 250 micrograms of r-hCG or 5,000 IU to 10,000 IU hCG should be administered 24-48 hours after the last Pergoveris injection. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination (IUI) may be performed.

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

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

Special populations

Older people

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

Renal and hepatic impairment

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

Paediatric population

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

Method of administration

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

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

4.3 Contraindications

Pergoveris is contraindicated in patients with:

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

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

- primary ovarian failure
- malformations of sexual organs incompatible with pregnancy
- fibroid tumours of the uterus incompatible with pregnancy

4.4 Special warnings and precautions for use

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

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

Porphyria

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

Treatment in women

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

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

Ovarian Hyperstimulation Syndrome (OHSS)

A certain degree of ovarian enlargement is an expected effect of controlled ovarian stimulation. It is more commonly seen in women with polycystic ovarian syndrome and usually regresses without treatment.

In distinction to uncomplicated ovarian enlargement, OHSS is a condition that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

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

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

Very rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events such as pulmonary embolism, ischaemic stroke or myocardial infarction.

Independent risk factors for developing OHSS include young age, lean body mass, polycystic ovarian syndrome, higher doses of exogenous gonadotrophins, high absolute or rapidly rising serum oestradiol level (> 900 pg/ml or $> 3,300$ pmol/l in anovulation), previous episodes of OHSS and large number of developing ovarian follicles (3 follicles of ≥ 14 mm in diameter in anovulation).

Adherence to recommended Pergoveris and FSH dosage and regimen of administration can minimise the risk of ovarian hyperstimulation. Monitoring of stimulation cycles by ultrasound scans as well as oestradiol measurements are recommended to early identify risk factors.

There is evidence to suggest that hCG plays a key role in triggering OHSS and that the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, if signs of OHSS occur such as serum oestradiol level $> 5,500$ pg/ml or $> 20,200$ pmol/l and/or ≥ 40 follicles in total, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or to use barrier contraceptive methods for at least 4 days. OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event. It most often occurs after hormonal treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. Therefore patients should be followed for at least two weeks after hCG administration.

If severe OHSS occurs, gonadotropin treatment should be stopped if still ongoing. The patient should be hospitalised and specific therapy for OHSS started. This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

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

Ovarian torsion

Ovarian torsion has been reported after treatment with other gonadotropins. This may be associated with other risk factors such as OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, previous or current ovarian cyst and polycystic ovarian syndrome. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion.

Multiple pregnancy

In patients undergoing induction of ovulation, the incidence of multiple pregnancies and births is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancy, especially high order, carry an increased risk of adverse maternal and perinatal outcomes. To minimise the risk of multiple pregnancy, careful monitoring of ovarian response is recommended.

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

Pregnancy loss

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

Ectopic pregnancy

Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after ART was reported to be higher than in the general population.

Reproductive system neoplasms

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

Congenital malformation

The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and multiple pregnancies.

Thromboembolic events

In women with recent or ongoing thromboembolic disease or women with generally recognised risk factors for thromboembolic events, such as personal or family history, thrombophilia or severe obesity (body mass index > 30 kg/m²), treatment with gonadotrophins may further increase the risk. In these women, the benefits of gonadotrophin administration need to be weighed against the risks. It should be noted however, that pregnancy itself as well as OHSS also carries an increased risk of thromboembolic events.

Sodium

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

Sucrose

Pergoveris contains 30 mg of sucrose per dose. This should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Pergoveris should not be administered as a mixture with other medicinal products, in the same injection, except follitropin alfa for which studies have shown that co-administration does not significantly alter the activity, stability, pharmacokinetic nor pharmacodynamic properties of the active substances.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

Pergoveris is not indicated during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are headache, ovarian cysts and local injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection).

Mild or moderate ovarian hyperstimulation syndrome (OHSS) has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

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

List of adverse reactions

Adverse reactions are listed below by MedDRA system organ class and by frequency. The frequency categories used are: very common ($\geq 1/10$), 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 ($< 1/10,000$).

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 suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

4.9 Overdose

Symptoms

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

Management

Treatment is directed to symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, gonadotropins. ATC code: G03GA30.

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

Mechanism of action

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

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

Pharmacodynamic effects

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

Clinical efficacy

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

5.2 Pharmacokinetic properties

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

Follitropin alfa

Distribution

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

Elimination

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

Lutropin alfa

Distribution

Following intravenous administration, lutropin alfa is rapidly distributed with an initial half-life of approximately one hour and eliminated from the body with a terminal half-life of about 10-12 hours. The steady state volume of distribution is around 10-14 l. Lutropin alfa shows linear pharmacokinetics, as assessed by AUC which is directly proportional to the dose administered.

Following subcutaneous administration, the absolute bioavailability is approximately 60%; the terminal half-life is slightly prolonged. The lutropin alfa pharmacokinetics following single and repeated administration of lutropin alfa are comparable and the accumulation ratio of lutropin alfa is minimal. The mean residence time is approximately 5 hours.

Elimination

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

Pharmacokinetic/pharmacodynamic relationships

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

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sucrose

Disodium phosphate dihydrate

Sodium dihydrogen phosphate monohydrate

Methionine

Polysorbate 20

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.

The package contains: 1 powder vial and 1 solvent vial.

6.6 Special precautions for disposal and other handling

For immediate and single use following first opening and reconstitution.

Reconstitution

The pH of the reconstituted solution is 6.5-7.5.

Pergoveris must be reconstituted with the solvent before use by gentle swirling.

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

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

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

7. MARKETING AUTHORISATION NUMBER

145-07-33159-00

8. REGISTRATION HOLDER

Merck Serono Ltd, 18 Hakishon, Yavne 81220

9. MANUFACTURER

Merck Serono S.A.

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The Ministry of Health determined the format of this leaflet and its content was checked and approved in February 2016