NAME OF THE MEDICINAL PRODUCT

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

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).

The reconstituted solution contains 150 IU r-hFSH and 75 IU r-hLH per milliliter. Follitropin alfa and lutropin alfa are produced in genetically engineered Chinese Hamster Ovary (CHO) cells.

PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

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

CLINICAL PARTICULARS

Therapeutic indications

Pergoveris is indicated for the stimulation of follicular development in adult women with severe LH and FSH deficiency.

Posology and method of administration

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

Pergoveris is intended for subcutaneous administration. The powder should be reconstituted immediately prior to use with the solvent provided.

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 on pharmacodynamic properties).

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 Special warnings and precautions for use).

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 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, seeSpecial precautions for disposal and other handling.

Contraindications

Pergoveris is contraindicated in patients with:
- hypersensitivity to the active substances or to any of the excipients listed in section List of excipients
- 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

Special warnings and precautions for use

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.

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.

Pergoveris contains 30 mg of sucrose per dose. This should be taken into account in patients with diabetes mellitus.
In clinical trials, lutropin alfa in combination with follitropin alfa has been shown to increase the ovarian sensitivity to gonadotropins. If an FSH dose increase is deemed appropriate, dose adaptation should preferably be at 7-14 day intervals and preferably with 37.5-75 IU increments using a licensed follitropin alfa preparation.

Ovarian Hyperstimulation Syndrome (OHSS) is a medical event distinct from uncomplicated ovarian enlargement. OHSS is a syndrome 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
• acute pulmonary distress, and thromboembolic events.

Very rarely, severe OHSS may be complicated by pulmonary embolism, ischemic stroke and myocardial infarction. Excessive ovarian response seldom gives rise to significant hyperstimulation unless hCG is administered to induce ovulation. Therefore in cases of ovarian hyperstimulation
it is prudent to withhold hCG in such cases and advise the patient to refrain from coitus or use barrier methods for at least 4 days. OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event, therefore patients should be followed for at least two weeks after hCG administration.

To minimise the risk of OHSS or of multiple pregnancy (see below), ultrasound scans as well as oestradiol measurements are recommended. In anovulation the risk of OHSS is increased by a serum oestradiol level > 900 pg/ml (3,300 pmol/l) and by the presence of more than 3 follicles of 14 mm or more in diameter.
Adherence to recommended Pergoveris and FSH dosage and regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and
multiple pregnancy (see below).

OHSS may be more severe and more protracted if pregnancy occurs. Most often, OHSS 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.

If severe OHSS occurs, gonadotrophin 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.
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. 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.

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

When risk of OHSS or multiple pregnancies is assumed, treatment discontinuation should be considered.

Women with a history of tubal disease are at risk ofectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after IVF was reported to be 2 to 5%, as compared to 1 to 1.5% in the general population.

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established

whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.

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.

In women with generally recognised risk factors for thrombo-embolic events, such as personal or family history, 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 also carries an increased risk of thrombo-embolic events.

Sodium

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

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.

Fertility, pregnancy and lactation

Pergoveris should not be used during pregnancy or lactation.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders	Very Common (≥1/10) Common (≥1/100 to <1/10)	Headache Somnolence
Respiratory, thoracic and mediastinal disorders	Very rare (<1/10,000)	Exacerbation or worsening of asthma
Gastrointestinal disorders	Common (≥1/100 to <1/10)	Abdominal pain and gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal cramps and bloating
Vascular disorders	Very rare (<1/10,000)	Thromboembolism, usually associated with severe ovarian hyperstimulation syndrome (OHSS)
General disorders and administration site conditions	Very Common (≥1/10)	Mild to severe injection site reaction (pain, redness, bruising, swelling and/ or irritation at the site of injection)

Reproductive	Reproductive	Reproductive
Reproductive system and breast disorders	Very Common (≥1/10)	Ovarian cysts
	Common (≥1/100 to <1/10)	Breast pain, pelvic pain, mild to moderate OHSS
	Uncommon (≥1/1,000 to <1/100)	Severe OHSS
	Rare (≥1/10,000 to <1/1,000)	Ovarian torsion, a complication of OHSS

Overdose

The effects of an overdose of Pergoveris are unknown. Nevertheless one could expect ovarian hyperstimulation syndrome to occur, which is further described in special warnings and precautions for use.

PHARMACOLOGICAL PROPERTIES

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.

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.

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.

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.

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 excreted in the urine.

Incompatibilities
This medicinal product must not be mixed with other medicinal products except follitropin alfa.

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

Pack Sizes
The product is supplied in pack sizes of 1, 3 and 10 vials with the corresponding number of 1, 3 and 10 vials of solvent.
Not all pack sizes may be marketed.

Special precautions for disposal and other handling
For single use only.
Pergoveris must be reconstituted with the solvent before use.
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.

If you administer Pergoveris to yourself, please carefully read the following instructions:

- Wash your hands. It is important that your hands and the items you use be as clean as possible.
- Assemble and lay out on a clean surface everything you need: one vial containing Pergoveris powder, one solvent vial, two alcohol swabs, one syringe, one needle for reconstitution and a fine bore needle for subcutaneous injection, sharp container
- Remove the protective cap from the solvent vial. Attach the reconstitution needle to the syringe and draw up some air into the syringe by pulling the plunger to approximately the 1 ml mark. Then, insert the needle into the vial, push the plunger to expel the air, turn the vial upside down and gently draw up all the solvent. Set the syringe down carefully on the work- surface taking care not to touch the needle.
- Prepare the injection solution: Remove the protective cap from the Pergoveris powder vial, pick up your syringe and slowly inject the solvent 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.
- Change the needle for the fine bore needle and remove any air bubbles: If you see air bubbles in the syringe, hold the syringe with the needle pointing upwards and gently flick the syringe until all the air collects at the top. Push the plunger until the air bubbles are gone.
- Immediately inject the solution: Your doctor or nurse will have already advised you where to inject (e.g. tummy, front of thigh). Wipe the chosen area with an alcohol swab. Firmly pinch the skin together and insert the needle at a 45° to 90° angle using a dart-like motion. Inject under the skin, as you were taught. Do not inject directly into a vein. Inject the solution by pushing gently on the plunger. Take as much time as you need to inject all the solution. Immediately withdraw the needle and clean the skin with an alcohol swab using a circular motion.

- Dispose of all used items: Once you have finished your injection, immediately discard all needles and empty glass containers in the sharp container provided. Any unused solution must be discarded.

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