PACKAGE INSERT

SCHEDULING STATUS: Schedule 4

PROPRIETARY NAME AND DOSAGE FORM:

Pergoveris 150 I.U. / 75 I.U Lyophilised pellet for solution

COMPOSITION:

Each vial contains 150 I.U (equivalent to 11 micrograms) of follitropin alfa (r-hFSH) and 75 I.U (equivalent to 3,0 micrograms) of lutropin alfa (r-hLH).

The reconstituted solution contains 150 I.U r-hFSH and 75 I.U r-hLH per millilitre.

Excipients: sucrose, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate. Methionine 0,1 mg/vial as antioxidant.

Solvent: Water for injection

PHARMACOLOGICAL CLASSIFICATION:

A21.10 Trophic Hormones

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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

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

Pharmacokinetic properties:

Combination of r-hFSH and r-hLH have shown the same pharmaco-kinetic profile as r-hFSH and r-hLH separately.

Follitropin alfa (r-hFSH)

Following intravenous administration, r-hFSH 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 and total clearance are 101 and 0,6 l/h, respectively. One-eighth of the r-hFSH dose is excreted in the urine.

Following subcutaneous administration, the absolute bioavailability is about 70 %.

Following repeated administration, r-hFSH accumulates 3-fold achieving a steady-state within 3-4 days.

Lutropin alfa (r-hLH)

Following intravenous administration, r-hLH 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. r-hLH shows linear pharmacokinetics, as assessed by AUC which is directly proportional to the dose administered.

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

The mean residence time is approximately 5 hours.

Following subcutaneous administration, the absolute bioavailability is approximately 60 %; the terminal half-life is slightly prolonged. The r-hLH pharmacokinetics following single and repeated administration of r-hLH are comparable and the accumulation ratio of r-hLH is minimal. There is no pharmacokinetic interaction with r-hFSH when administered simultaneously.

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.

CONTRAINDICATIONS:

Pergoveris is contraindicated in patients with:

- Hypersensitivity to the active substances r-hFSH and r-hLH or to any of the excipients.
- Tumours of the hypothalamus and pituitary gland.
- Ovarian enlargement or cyst not due to polycystic ovarian disease.
- Gynaecological haemorrhage of unknown aetiology.
- Ovarian, uterine or mammary carcinoma.
- Pergoveris should not be used in a pregnant woman or in a woman who is breastfeeding her infant (see PREGNANCY AND LACTATION).

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.

WARNINGS and SPECIAL PRECAUTIONS:

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

Gonadotropin therapy requires a certain time commitment by medical practitioners and supportive health 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.

Self-administration of Pergoveris should only be performed by patients who are well motivated, adequately trained and with access to expert advice.

The first injection of Pergoveris should be performed under medical supervision.

Patients with porphyria or a family history of porphyria should be closely monitored during treatment with Pergoveris. Deterioration or a first appearance of this condition may require cessation of treatment.

Pergoveris contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium-free”.
Pergoveris contains 30 mg of sucrose per dose. This should be taken into account in patients with diabetes mellitus.

Before starting treatment, the (couple’s) infertility should be assessed as diagnosis of Hypogonadotrophic hypogonadism must be confirmed.
Other possible causes such as

- Hypothyroidsm
- Adrenocortical deficiency
- Hyperprolactinaemia and pituitary or hypothalamic tumours must be excluded.

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

In clinical trials, r-hLH in combination with r-hFSH has been shown to increase the ovarian sensitivity to gonadotropins. If an FSH dose increase is deemed appropriate, dose adaption should preferably be at 7 – 14 day intervals and preferably with 37,5 – 75 IU increments using a registered r-hFSH preparation.

Ovarian Hyperstimulation Syndrome (OHSS) is a medical event distinct from uncomplicated ovarian enlargement. OHSS must be avoided. 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 peritoneal, pleural and, rarely, in the pericardial cavities.

The following symptomatology may be observed in cases of OHSS:
Mild manifestations of OHSS includes:

- Abdominal pain
- Abdominal distension

Severe manifestations of OHSS includes:

- Severe ovarian enlargement
- Weight gain
- Dyspnoea
- Oliguria and moderate OHSS may present with:

Gastrointestinal symptoms such as nausea, vomiting and diarrhoea.

Clinical evaluation may reveal:

- Hypovolaemia
- Haemoconcentration
- Electrolyte imbalances
- Ascites
- Haemoperitoneum
- Pleural effusions
- Hydrothorax
- Acute pulmonary distress, and thromboembolic events

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, the use of higher doses of Pergoveris, high absolute or rapidly rising serum oestradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in ART cycles.

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 Pergoveris 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, Pergoveris 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 patient 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 following natural conception.
When risk of OHSS or multiple pregnancies is assumed, treatment discontinuation should be considered.

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 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 treatment regimens with Pergoveris 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 is higher than after spontaneous conceptions.

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.

Effects on ability to drive and use machines:

The ovarian hyperstimulation syndrome and associated symptoms may impair the patient's ability to drive or to use machines.

INTERACTIONS:

Pergoveris should not be administered as a mixture with other medicines, in the same injection, except r-hFSH.

PREGNANCY AND LACTATION:

Pergoveris should not be used during pregnancy or lactation. (See CONTRAINDICATIONS).

During lactation, the secretion of prolactin can result in a poor prognosis to ovarian stimulation.
Women should not breastfeed their infants while receiving Pergoveris.

DOSAGE AND DIRECTIONS FOR USE:

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

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

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 r-hLH may be insufficient.

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 registered r-hFSH 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 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.
In clinical trials, patients with severe FSH and LH deficiency were defined by an endogenous serum LH level < 1,2 IU/l and FSH less 5 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 %.

SIDE EFFECTS:

The following definitions apply to the frequency terminology used hereafter:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000

Immune system Disorders

Very rare: Mild to severe systemic allergic reactions (e.g. erythema, rash, facial swelling, urticaria, oedema, difficulty breathing). Serious cases of allergic reactions, including anaphylactic reactions and shock, have also been reported

Nervous System Disorders

Very common: Headache

Vascular Disorders

Very rare: Thromboembolism such as pulmonary embolism, ischaemic stroke or myocardial infarction, usually associated with severe ovarian hyperstimulation syndrome (OHSS)

Respiratory, thoracic and mediastinal Disorders

Very rare: Exacerbation or worsening of asthma

Gastrointestinal Disorders

Common: Abdominal pain and gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal discomfort and abdominal distension

Reproductive system and breast Disorders

Very common: Ovarian cysts

Common: Breast pain, pelvic pain, mild to moderate OHSS

Uncommon: Severe OHSS

Rare: Complications of OHSS Incl. (tense) ascites, pleural effusion, acute respiratory distress syndrome, ovarian torsion.

General Disorders and administration site conditions

Very common: Mild to severe injection site reaction (pain, redness, bruising, swelling and/or irritation at the site of injection)

KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULAR OF ITS TREATMENT:

The effects of an overdose of Pergoveris are unknown. OHSS may occur. (See WARNINGS and SPECIAL PRECAUTIONS).

IDENTIFICATION:

Pergoveris is presented as a pellet and solvent for solution for injection.

The pellet is white to off-white lyophilized.

The solvent is a clear colourless solution.

PRESENTATION:

Pellet: 3 ml clear colourless glass vials with a grey rubber stopper and aluminium flip-off cap.

Solvent: 3 ml clear colourless glass vials with a Teflon coated grey rubber stopper and aluminium Flip-off cap.

The medicinal product is supplied in pack sizes* of 1, 3 and 10 vials with the corresponding number of 1, 3 and 10 vials of solvent in a cardboard carton.

* Only the marketed pack sizes will appear on the printed leaflet.

STORAGE INSTRUCTIONS:

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. Discard any unused portion after initial opening.

Pergoveris may be mixed with r-hFSH and co-administered as a single injection.

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

Keep out of the reach of children.

Store at or below 25 °C. Store in the original package in order to protect from light.

REGISTRATION NUMBER:

44/21.10/0781

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Merck (Pty) Ltd

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