Pergoveris®
Follitropin alfa/Lutropin alfa

1 QUALITATIVE AND QUANTITATIVE COMPOSITION

- Pergoveris (300 IU + 150 IU)/0.48 mL solution for injection in pre-filled pen: 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.
- Pergoveris (900 IU + 450 IU)/1.44 mL solution for injection in pre-filled pen: 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 5.1.

2 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.

3 CLINICAL PARTICULARS

3.1 Therapeutic indications

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

3.2 Posology and method of administration

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

Pergoveris is intended for subcutaneous administration. The injection site should be alternated daily.

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 these patients are amenorrhoeic and have low endogenous estrogen 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 4.1 Pharmacodynamic properties).

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

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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 choriogonadotropin alfa (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 hormones 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 3.4 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 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 5.6 Special precautions for disposal and other handling.

3.3 Contraindications

Pergoveris is contraindicated in patients with:

- hypersensitivity to the active substances follitropin alfa and lutropin alfa or to any of the excipients listed in section 5.1 List of excipients
- case of tumours of the hypothalamus and pituitary gland
- ovarian enlargement or cyst not due to polycystic ovarian disease
- gynaecological haemorrhages of unknown aetiology
- 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

3.4 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 the following:

- Hypothyroidism
- Adrenocortical deficiency
- Hyperprolactinemia and pituitary or hypothalamic tumours

Appropriate specific treatment should be given.

Gonadotropin therapy requires a certain time commitment by physicians 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 and exaggerated response in others. 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 direct medical supervision.

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.

Mild manifestation of OHSS include abdominal pain, abdominal discomfort and distention, and enlarged ovaries. Moderate OHSS may additionally present with nausea, vomiting, ultrasound evidence of ascites and marked ovarian enlargement.

Severe OHSS further includes symptoms such as severe ovarian enlargement, weight gain, dyspnoea or oliguria. Clinical evaluation may reveal signs such as hypovolaemia,

haemoconcentration, electrolyte imbalances, ascites, pleural effusions, or acute pulmonary distress and thromboembolic events, haemoperitonium, hydrothorax.

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

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 advise the patient to refrain from coitus or use barrier contraceptive 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.

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.

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, it is recommended that gonadotropin treatment be stopped if still ongoing. The patient should be hospitalized and specific therapy for OHSS started.

This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

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 pregnancies
In patients undergoing induction of ovulation, the incidence of multiple pregnancies 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.

Pregnancy loss
The incidence of pregnancy loss 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.

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 neoplasm
There have been reports of ovarian and other reproductive system neoplasm, 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 gonadotropins increases the risk of these tumours in infertile women.

Congenital anomalies
The prevalence of congenital anomalies after the use of ART may be slightly higher than after spontaneous conceptions although it is unclear whether this is related to factors inherent to the couple's infertility or the ART procedures. Based on clinical trials and postmarketing data there is no evidence that gonadotropin use increases the risk of congenital anomalies in the offspring of the patients receiving infertility treatments.

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 for aggravation or occurrence of such events. 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".

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

3.5 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.

No other clinically significant drug interaction has been reported during Pergoveris therapy.

3.6 Fertility, pregnancy and lactation
Pergoveris should not be used during pregnancy or lactation.

Fertility
Pergoveris is indicated for use in fertility (see therapeutic indications).

3.7 Effects on ability to drive and use machines

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

3.8 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 *3.4 Special warning and precautions for use*).

Thromboembolism may occur very rarely, usually associated with severe OHSS (see section *3.4 Special warning and precautions for use*).

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA system organ class and by frequency. The frequency categories used are: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Immune system disorders

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

Nervous system disorders

Very common: Headache

Vascular disorders

Very rare: Thromboembolism, 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, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhoea.

Reproductive system and breast disorders

Very common: Ovarian cysts
Common: Mild or moderate OHSS (including associated symptomatology), breast pain, pelvic pain
Uncommon: Severe OHSS (including associated symptomatology)
Rare: Complication of severe OHSS.

General disorders and administration site conditions

Very common: Mild to severe injection site reaction (e.g pain, erythema, 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.

3.9 Overdose

Symptoms

The effects of an overdose of Pergoveris are unknown. Nevertheless one could expect ovarian hyperstimulation syndrome to occur, which is further described in section 3.4 Special warnings and precautions for use.

Management

Treatment is directed to symptoms.

4 PHARMACOLOGICAL PROPERTIES

4.1 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 less than 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 Pergoveris containing less than 75 IU r hLH daily may provide too little LH-activity to ensure adequate follicular development.

4.2 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 3-4 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.

4.3 Preclinical safety data

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

5 PHARMACEUTICAL PARTICULARS

5.1 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

5.2 Incompatibilities
Not applicable

5.3 Shelf-life
The expiry date is indicated on the packaging.

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.

5.4 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 *5.3 Shelf life*.

5.5 Nature and Contains 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.
- 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.

5.6 Special precautions for disposal and other handling
Only clear solution without particles should be used.

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

For instructions on the use of this medicinal product, see the package leaflet, and the 'Instruction for use'

5.7 Package Quantities and Registration Numbers
Pergoveris (300 IU + 150 IU)/0.48 mL, Box, 1 pre-filled pen + 5 injection needles, Reg No. DKI1980501743A1
Pergoveris (900 IU + 450 IU)/1.44 mL, Box, pre-filled pen + 14 injection needles, Reg No. DKI1980501743B1

6. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 21 Mar 2019.
Date of last renewal : 14 Jan 2024.

7. DATE OF REVISION OF THE TEXT

BPOM Approval of the Update xxxxxx.

8. CLASSIFICATION OF MEDICINE

Medicinal product subject to medical prescription. Obat Keras.

HARUS DENGAN RESEP DOKTER

Manufactured by
Merck Serono S.p.A.,
Modugno, Italy

Imported by
PT Merck Tbk,
Jakarta, Indonesia

Pada proses pembuatannya bersinggungan dengan bahan yang bersumber babi.

PI based on CCDS version 5.0 (28-Oct-2021)