SUMMARY OF PRODUCT CHARACTERISTICS

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 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.

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/m^2), 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 (≥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 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

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 3-4 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

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 Serono Ltd

5 New Square

Bedfont Lakes Business Park

Feltham

Middlesex

TW14 8HA

UK

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 11648/0276

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

05/07/2023