PRODUCT MONOGRAPH

Pr PERGOVERIS®

follitropin alfa/lutropin alfa (150 IU:75 IU)

Powder and Diluent for Solution for Injection

Solution for Injection in a Pre-filled Pen
(300 IU/150 IU in 0.48 mL; 450 IU/225 IU in 0.72 mL; 900 IU/450 IU in 1.44 mL)

Therapeutic Classification: Gonadotropin

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® Ares Trading S.A.

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Subcutaneous injection (SC)	Lyophilized powder for reconstitution with 1 mL sterile water for injection / 150 IU of r-hFSH and 75 IU of r-hLH Solution for injection in a pre-filled pen: 300 IU r-hFSH/150 IU r-hLH in 0.48 mL; 450 IU r-hFSH/225 IU r-hLH in 0.72 mL; 900 IU r-hFSH/450 IU r-hLH in 1.44 mL.	There are no clinically relevant non-medicinal ingredients. *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

DESCRIPTION

PERGOVERIS (follitropin alfa/lutropin alfa [150 IU:75 IU]) is a fixed dose combination product which contains 150 IU of recombinant human follicle stimulating hormone (r-hFSH; INN: Follitropin alfa) and 75 IU of recombinant human luteinizing hormone (r-hLH; INN: Lutropin alfa).

The recombinant follitropin alfa and lutropin alfa are human glycoprotein hormones produced through genetic modification of a Chinese hamster ovary (CHO) cell line. (For more information on production of follitropin alfa and lutropin alfa, refer to the Product Monographs for GONAL-f® and LUVERIS® respectively.)

INDICATIONS AND CLINICAL USE

PERGOVERIS (follitropin alfa/lutropin alfa [150 IU:75 IU]) is indicated for stimulation of follicular development in hypogonadotropic hypogonadal women with severe LH deficiency (LH < 1.2 IU/L) and FSH deficiency (≤ 5.0 IU/L) who are candidates for concurrent therapy with FSH and LH.

CONTRAINDICATIONS

PERGOVERIS (follitropin alfa/lutropin alfa [150 IU:75 IU]) is contraindicated in patients with:

- Hypersensitivity to the active substances follitropin alfa and lutropin alfa or to any of the excipients or component of the container. For a complete listing, see the *DOSAGE FORMS, COMPOSITION AND PACKAGING* section of the Product Monograph.
- Primary ovarian failure or anovulation with normal levels of LH and FSH
- Uncontrolled thyroid or adrenal dysfunction
- Tumours of the hypothalamus or pituitary gland
- Ovarian enlargement or cyst of undetermined origin
- Gynecological hemorrhages of undetermined origin
- Sex hormone dependent tumours of the reproductive tract and accessory organs
- Current pregnancy or lactation

WARNINGS AND PRECAUTIONS

General:

PERGOVERIS (follitropin alfa/lutropin alfa [150 IU:75 IU]) 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.

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

Information for Patients:
PERGOVERIS is a combination of GONAL-f and LUVERIS at a fixed dose of 150 IU of FSH and 75 IU LH in a 2:1 ratio. Prior to therapy with PERGOVERIS, patients should be informed of the duration of treatment and need for monitoring. The risks of ovarian hyperstimulation syndrome in women (see WARNINGS AND PRECAUTIONS, Overstimulation of the Ovary) and other possible adverse reactions (see ADVERSE REACTIONS) should be discussed.

Selection of Patients:

1. Before starting PERGOVERIS therapy, a thorough gynecologic and endocrinologic evaluation must be performed. This should include an assessment of pelvic anatomy and exclusion of pregnancy.
2. Hypogonadotropic hypogonadism should be confirmed. Patients should have baseline serum hormone levels of LH < 1.2 IU/L and FSH < 5 IU/L and a negative progestin challenge test.
3. Patients in later reproductive life have a greater predisposition to endometrial carcinoma as well as a higher incidence of anovulatory disorders. A thorough diagnostic evaluation should always be performed in patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities.

Overstimulation of the Ovary:

Ovarian Enlargement

Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain may occur in patients treated with gonadotropins, such as PERGOVERIS. These conditions generally regress without treatment within two or three weeks. Careful monitoring of ovarian response can minimize the risk of overstimulation.

Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a medical event distinct from uncomplicated ovarian enlargement. 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 early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain.

OHSS can manifest itself with increasing degrees of severity. Mild manifestations of OHSS include abdominal pain, abdominal discomfort and distension 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, dyspnea or oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, pleural effusions, or acute pulmonary distress. Very rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events, such as pulmonary embolism, ischemic stroke or myocardial infarction (see WARNINGS AND PRECAUTIONS, Respiratory and Cardiovascular). Transient liver function test abnormalities suggestive of hepatic dysfunction have been reported in association with OHSS.

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 estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

OHSS may be more severe and more protracted if pregnancy occurs. OHSS develops rapidly; therefore, patients should be followed for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum severity at seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If there is evidence that OHSS may be developing prior to hCG administration, hCG must be withheld.

If severe OHSS occurs, treatment with gonadotropins must be stopped and the patient should be hospitalized. A physician who is experienced in the management of fluid/electrolyte imbalances and/or OHSS should be consulted.

Patients should be counselled to recognize signs and symptoms of hyperstimulation, as OHSS can quickly progress to become a serious medical event.

In 6 clinical trials, 102 hypogonadotropic hypogonadal patients were initially assigned in receiving LH 75IU. Overall there were a total of 204 treatment cycles with concurrent/co-administration of 150 IU FSH and 75 IU LH for the purpose of follicular development, moderate or severe OHSS was reported in 6/204 (2.9%) treatment cycles.

Carcinogenesis and Mutagenesis

Long-term studies to evaluate the carcinogenic potential of PERGOVERIS or its constituent drugs LUVERIS and GONAL-f have not been performed. 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. The causality of these neoplasms has not been established.

Multiple Pregnancies

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

In patients undergoing ART procedures the risk of a multiple pregnancy are related mainly to the number of embryos transferred, their quality and the patient age.

The patients should be advised of the potential risk of multiple births before starting treatment.

Patients should be informed of options available in the case of over-stimulation (e.g., egg retrieval and embryo transfer through ART, or cycle cancellations) and the need to abstain from unprotected intercourse.

Discontinuation

In cases where more than two follicles are mature before triggering ovulation, treatment discontinuation or conversion to ART should be considered.

Ectopic Pregnancy

Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is a product of spontaneous conception or of 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 gonadotropins increases the baseline risk of these tumours in infertile women.

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.

Congenital Anomalies

The prevalence of congenital anomalies after the use of ART may be slightly higher than from spontaneous conceptions although it is unclear whether this is related to factors inherent to the couple's infertility or the ART procedures.

Hematologic

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.

Respiratory and Cardiovascular

The following paragraph describes serious medical events reported following gonadotropin therapy.

Serious pulmonary conditions (e.g., atelectasis, acute respiratory distress syndrome and exacerbation of asthma) have been reported. In addition, thromboembolic events both in association with, and separate from OHSS have been reported. Intravascular thrombosis and embolism can result in reduced blood flow to critical organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, myocardial infarction, cerebral vascular occlusion (ischemic stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

In women with recent or ongoing thromboembolic disease or women with generally recognized risk factors for thromboemoblic events, such as personal or family history, 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 thrombo-embolic events.

Special Populations

Pregnant Women: PERGOVERIS should not be used during pregnancy. (See CONTRA-INDICATIONS)

Nursing Women: PERGOVERIS should not be used during lactation. (See CONTRA-INDICATIONS)

Pediatrics: Not indicated for treatment in pediatric population.

Geriatrics: Not indicated for treatment in the geriatric population.

ADVERSE REACTIONS

The safety of PERGOVERIS (follitropin alfa/lutropin alfa for injection [150 IU:75 IU]) powder for injection is based on 6 clinical trials in which the two component drugs, follitropin alfa and lutropin alfa, were given concurrently or combined in a single injection to women with hypogonadotropic hypogonadism.

Overall, treatment with either PERGOVERIS powder for injection or solution for injection is considered safe and well tolerated in the studied population. The safety and tolerability profile of the liquid formulation was similar to that of the powder formulation of PERGOVERIS.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of concurrent or combined use in a single injection of follitropin alfa and lutropin alfa was examined in six clinical studies that treated 170 women with hypogonadotropic hypogonadism. Among all these patients, there are 204 treatment cycles with administration of 75 IU LUVERIS and 150 IU GONAL-f. Summary table of adverse drug reactions from controlled trials following concurrent/co-administration of 150 IU FSH and 75 IU LH with incidence rate ≥ 1% is presented in Table 1 below.

Table 1: Adverse Events Reported in ≥1% Patients in All Cycles in All Hypogonadotropic Hypogonadal Patients in Studies 6253, 6905[(a)], 7798[(b)], 8297[(c)], 21008, and 21415

Study	6253	6905	7798	8297	21008	21415
Trial description	Phase II/III open-label, randomized, dose-finding, comparative, parallel group, multicentre study, n=38	Phase II/III open-label, randomized, dose-finding, comparative, parallel group, multicentre study, n=40	Phase III randomized, dose-finding, multicentre study, n=15	Phase III non-comparative, multicentre study, n=38	Phase III prospecitve, randomized, controlled, double-blind, multicentre study, n=39	Phase III open-label, non-comparative, multicentre study, n=31
Number of treatment cycles with LH 75IU + FSH 150 IU	16	16	12	80	26	54
Headache	3 (18.8%)	1 (6.3%)		1 (1.3%)	4 (15.4%)	3 (5.6%)
Nausea	1 (6.3%)	1 (6.3%)		1 (1.3%)	2 (7.7%)	2 (3.7%)
Ovarian hyperstimulation	1 (6.3%)		1 (8.3%)	3 (3.8%)	0	1 (1.9%)
Breast pain female	2 (12.5%)	2 (12.5%)				2 (3.7%)
Abdominal pain		1 (6.3%)			4 (15.4%)	2 (3.7%)
Ovarian cyst					1 (3.8%)	1 (1.9%)
Flatulence		0			1 (3.8 %)	5 (9.3%)
Injection site reaction		0			2 (7.7%)	2 (3.7%)
Dysmenorrhea		2 (12.5%)				
Ovarian disorder	1 (6.3%)					1 (1.9%)
Diarrhea	1 (6.3%)				0	1 (1.9%)
Constipation					1 (3.8 %)	2 (3.7%)
Pain	2 (12.5%)	0				1 (1.9%)
Fatigue		1 (6.3%)			1 (3.8%)	1 (1.9%)
Upper respiratory tract infection		0				1 (1.9%)

The most common adverse events reported were abdominal pain, breast pain, constipation, dysmenorrhea, flatulence, headache, nausea, ovarian cyst, and pelvic pain, which were typical of agents in this therapeutic class and not unexpected.

Post-Market Experience

The following adverse reactions have been identified during post-approval of PERGOVERIS powder for injection (in Europe) or concurrent use of GONAL-f and LUVERIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to PERGOVERIS exposure.

Immune system disorders: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Nervous system disorders: Headache

Vascular disorders: Thromboembolism may occur very rarely, usually associated with severe OHSS

Respiratory, thoracic and mediastinal disorders: Exacerbation or aggravation of asthma

Gastrointestinal disorders: Abdominal pain, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhea

Reproductive system and breast disorders: Ovarian cysts, breast pain, pelvic pain, complications of severe OHSS. Mild or moderate OHSS has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon.

General disorders and administration site conditions: Injection site reactions

DRUG INTERACTIONS

Drug-Drug Interactions

No drug interaction trials have been conducted using PERGOVERIS (follitropin alfa/lutropin alfa [150 IU:75 IU]). The pharmacokinetics (PK) of lutropin alfa and follitropin alfa were unaffected when lutropin alfa and follitropin alfa were administered together versus each agent dosed alone (See Part II, DETAILED PHARMACOLOGY).

Drug-Food Interactions

Interactions with food have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Treatment with PERGOVERIS (follitropin alfa/lutropin alfa [150 IU:75 IU]) should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

In clinical trials, lutropin alfa in combination with follitropin alfa has been shown to increase the ovarian sensitivity to gonadotropins.

When using PERGOVERIS powder for injection, the powder should be reconstituted immediately prior to use with the diluent provided.

Recommended Dose and Dosage Adjustment

PERGOVERIS is intended for subcutaneous administration.

In LH and FSH deficient women (hypogonadotropic 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 gonadotropin (hCG). PERGOVERIS should be given as a course of daily injections. Since these patients are amenorrheic and have low endogenous estrogen 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 estrogen response. A recommended regimen commences with one dose of PERGOVERIS (containing 150 IU r-hFSH/75 r-hLH) daily. If less than the daily recommended dose is used, the follicular response may be unsatisfactory because the amount of lutropin alfa 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 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 µg r-hCG or 5,000 IU to 10,000 IU urinary 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.

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%.

Missed Dose

If a dose is missed, do not take a double dose to make up for the missed dose. In this case, a healthcare professional should be consulted.

Administration

PERGOVERIS is intended for subcutaneous administration. The injection site should be alternated daily. Self-administration of PERGOVERIS should only be performed by patients who have been prescribed the medication by a licensed fertility specialist.

PERGOVERIS powder and diluent for solution for injection

For reconstitution and administration instructions for the powder and diluent for solution for injection, see PART III: CONSUMER INFORMATION section.

PERGOVERIS solution for injection in a pre-filled pen

PERGOVERIS solution for injection is available in pre-filled pens that can deliver 2 doses, 3 doses, or 6 doses of 150 IU follitropin alfa and 75 IU lutropin alfa.

For administration and instructions on how to use the pre-filled pen, see PART III: CONSUMER INFORMATION section.

OVERDOSAGE

The effects of an overdose of PERGOVERIS (follitropin alfa/lutropin alfa [150 IU:75 IU]) are unknown, nevertheless there is a possibility that OHSS may occur, which is further described in WARNINGS AND PRECAUTIONS, Overstimulation of the Ovary section of the Product Monograph.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PERGOVERIS (follitropin alfa/lutropin alfa [150 IU:75 IU]) is fixed dose combination product of recombinant human follicle stimulating hormone (FSH) and recombinant human luteinizing hormone (LH). FSH and LH are the primary hormones responsible in folliculogenesis and ovulation. FSH is involved in the initiation of follicular development through its effects on the granulosa cells of the developing ovarian follicle, while LH stimulates theca cells to secrete androgens. Androgens are used by granulosa cell aromatase enzymes to produce estradiol, thus supporting FSH-induced follicular development. Co-administration of FSH with LH is expected to stimulate development of a potential follicle and to indirectly prepare the reproductive tract for implantation and pregnancy in women with LH and FSH deficiency.

Pharmacodynamics

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 estradiol secretion by the follicles, the growth of which is stimulated by FSH.

Pharmacokinetics

The pharmacokinetics of follitropin alfa and lutropin alfa have been described in studies that were conducted as part of their respective development programs. For individual pharmacokinetic profiles of follitropin alfa and lutropin alfa, refer to Product Monographs for GONAL-f and LUVERIS.

PERGOVERIS reconstituted powder is bioequivalent to 150 IU follitropin alfa plus 75 IU lutropin alfa following single-dose mixed administration in healthy female subjects (N = 42) who had been down-regulated with oral contraceptive pills prior to subcutaneous injection of 900 IU r-hFSH and 450 IU r-hLH (see Figures 1 and 2).

Figure 1: Mean Concentration-Time Profiles of FSH Concentrations (IU/L) in Serum (n=42), Linear Scale

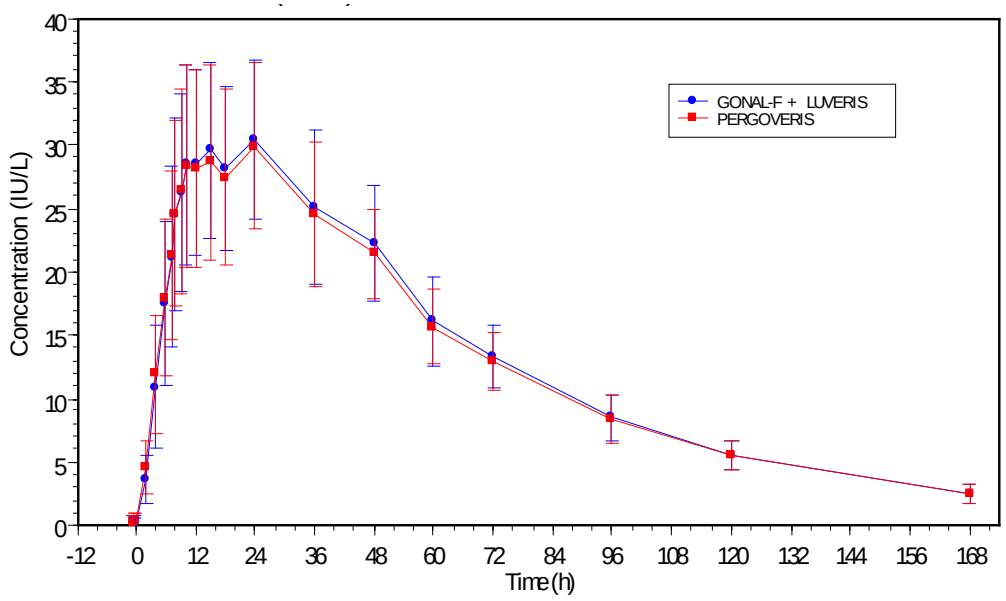
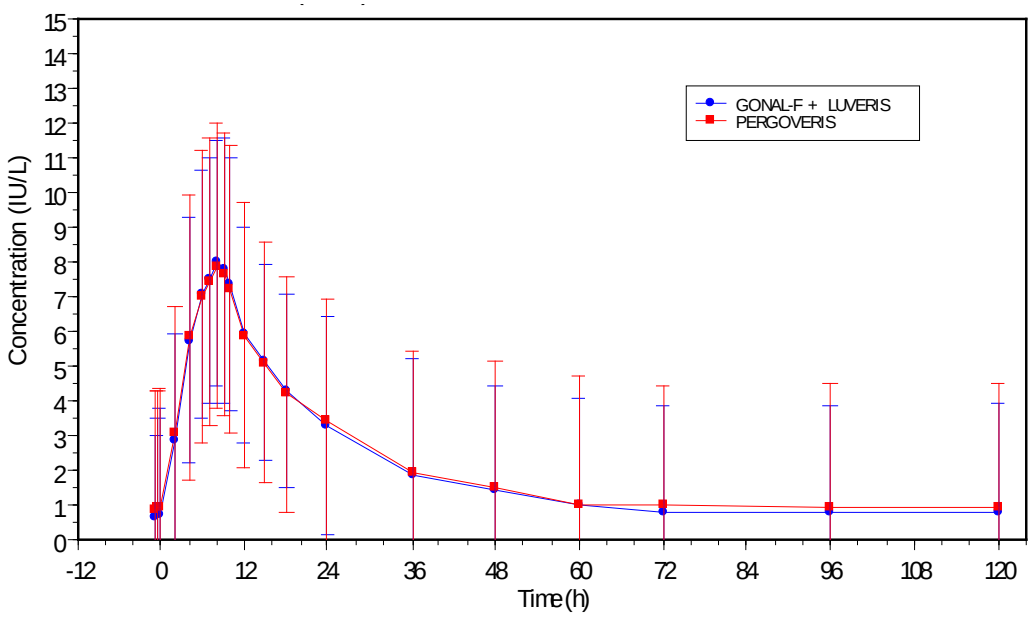


Figure 2: Mean Concentration-Time Profiles of LH Concentrations (IU/L) in Serum (n=44) Linear Scale



An overview of the PK parameters of FSH and LH after SC administration of PERGOVERIS and r-hLH and r-hFSH mixed are shown in Table 2 (Trial EMR200061-004). The 90% confidence intervals of the ratios of the means of C_{max} and $AUCt_{last}$ for the two analytes FSH and LH were within the pre-defined range (0.8-1.25), thus bioequivalence of r-hFSH r-hLH fixed 2:1 monodose combination (PERGOVERIS, test) and GONAL-f and LUVERIS (reference) can be concluded.

Table 2: Pharmacokinetic parameters of r-hFSH and r-hLH (Geomean, GeoCV% and Range) after single-dose SC administration of PERGOVERIS vs. co-administration of GONAL-f and LUVERIS in pituitary desensitized healthy female subjects

	FSH		LH	
Parameter	**GONAL-f + LUVERIS (N = 42)**	**PERGOVERIS (N = 42)**	**GONAL-f + LUVERIS (N = 42)**	**PERGOVERIS (N = 42)**
$\_^* C_{max}$ (IU/L)	30.69 (22.7) 16.03 – 44.74	30.17 (26.8) 15.93 – 51.13	7.33 (27.9) 2.82 – 12.26	6.85 (32.5) 2.74 – 11.13
$\_^* AUC_{0-t}$ (IU/L*h)	2071 (20.3) 1188 – 2882	2051 (19.7) 1249 – 2947	137 (35.9) 36 – 418	132 (32.3) 56 – 215
t_{max} [1] (h)	15.1 7.0 – 36.5	23.3 9.0 – 35.7	8.0 6.0 – 10.1	8.0 6.0 – 10.0
$t_{1/2}$ (h)	39.8 (13.9) 33.9 – 69.2	39.9 (12.2) 31.3 – 61.4	13.9 (40.3) 7.6 – 48.0	14.6 (44.9) 8.1 – 38.9
CL/f (L/h)	0.40 (19.6) 0.28 – 0.67	0.40 (20.2) 0.26 – 0.67	2.51 (66.9) 0.18 – 7.81	2.52 (75.4) 0.15 – 6.82

*Baseline adjusted [1]median and range; IU = international units; AUC = area under the curve; CL/f = apparent clearance

PERGOVERIS reconstituted powder and solution for injection formulations show bioequivalence following single-dose administration in healthy female subjects (N=34) who had been down-regulated with oral contraceptive pills prior to subcutaneous injection of PERGOVERIS reconstituted lyophilized powder (LP) or PERGOVERIS solution for injection (liquid, 900 IU r-hFSH/450 IU r-hLH) (Trial EMR200061-006).

Out of the 34 subjects randomized and dosed, 22 were included in the PK analysis set. Four (4) subjects were excluded due to incomplete data, and 8 subjects were excluded because successful downregulation was not confirmed.

An overview of the pharmacokinetic parameters of the PERGOVERIS reconstituted powder after SC administration and PERGOVERIS solution for injection are shown in Table 3 (Trial EMR200061-006). The 90% confidence intervals of the ratios of the means of C_{max} and AUC_{0-t} for the two analytes FSH and LH were within the pre-defined range (0.8 – 1.25) and therefore bioequivalence of the two formulations was demonstrated.

Table 3: Pharmacokinetic Parameters of r-hFSH and r-hLH (Geomean, GeoCV% and Range) after single-dose SC administration of PERGOVERIS reconstituted powder vs. PERGOVERIS solution for injection

	FSH		LH	
Parameter	**PERGOVERIS reconstituted powder (N = 22)**	**PERGOVERIS solution for injection (N = 22)**	**PERGOVERIS reconstituted powder (N = 22)**	**PERGOVERIS solution for injection (N = 22)**
C_{max} . adj (IU/L)	42.55 (29.0) 22.6-77.6	47.92 (27.3) 27.5 – 88.3	9.782 (24.1) 6.38 – 17.78	10.126 (31.1) 6.00 – 18.58
AUC_{0-t} , adj (IU/L*h)	2775.4 (22.0) 1809 - 4242	3187.4 (24.3) 1921 - 5200	195.2 (22.5) 122 - 287	210.4 (25.8) 136 - 333
t_{max} [1] (h)	16.575 9.00 – 36.12	23.983 8.23 – 36.00	7.725 3.98 – 10.03	8.000 6.03 – 12.00
$t_{1/2}$ (h)	35.31 (10.0) 30.8 – 45.6	36.87 (14.2) 30.2 – 55.3	13.608 (25.5) 8.13 – 24.57	12.507 (17.1)* 9.27 – 18.92
CL/f (L/h)	0.3091 (22.2) 0.202 – 0.467	0.2673 (24.2) 0.166 – 0.440	2.238 (21.2) 1.54 – 3.38	2.082 (25.2) 1.36 – 3.16

[1] = median and range, data were from observed data; * N = 21; IU is international units; AUC is area under the curve; CL/f is apparent clearance.

Special populations

Pharmacokinetics of PERGOVERIS in the geriatric or pediatric populations or in patients with renal or hepatic insufficiency have not been established.

STORAGE AND STABILITY

PERGOVERIS (follitropin alfa/lutropin alfa for injection [150 IU:75 IU]) powder and diluent for solution for injection
For immediate and single use following first opening and reconstitution.

Do not store above 25°C. Avoid freezing. Store in the original package in order to protect from light. Please refer to the expiration date imprinted on the product outer and inner labels.

PERGOVERIS (follitropin alfa/lutropin alfa injection [150 IU:75 IU]) solution for injection in a pre-filled pen
Store in a refrigerator (2°- 8°C). Avoid freezing. Store in the original package in order to protect from light. Please refer to the expiration date imprinted on the product outer and inner labels.

Once opened, the product may be stored for up to 28 days at or below 25°C.

SPECIAL HANDLING INSTRUCTIONS

PERGOVERIS (follitropin alfa/lutropin alfa for injection [150 IU:75 IU]) powder and diluent for solution for injection

For single use only. It must not be mixed with other medicinal products except those mentioned below.

PERGOVERIS powder must be reconstituted with the diluent before use.

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

PERGOVERIS must not be administered as a mixture with other medicinal products in the same injection; PERGOVERIS powder for injection may be mixed with follitropin alfa and co-administered as a single injection.

PERGOVERIS (follitropin alfa/lutropin alfa injection [150 IU:75 IU]) solution for injection in a pre-filled pen

Only clear solution without particles should be used.

Needles should not be re-used or used if seal on needle cap has been broken.

PERGOVERIS must not be administered as a mixture with other medicinal products in the same injection. PERGOVERIS solution for injection may be administered concomitantly with follitropin alfa as separate injections.

For detailed instructions on the use of PERGOVERIS, see PART III: CONSUMER INFORMATION section.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

PERGOVERIS powder and diluent for solution for injection

PERGOVERIS (follitropin alfa/lutropin alfa for injection [150 IU:75 IU]) is presented as a powder and diluent for injection. The powder is presented in 3 mL vials (Type I glass) with stopper (bromobutyl rubber), aluminium seal ring and flip-off cap. The diluent for reconstitution is presented in 3 mL vials (Type I glass) with a Teflon-coated rubber stopper (latex-free), an aluminium seal ring and a flip-off cap.

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

One vial of powder contains 150 IU (equivalent to 11 micrograms) of follitropin alfa and 75 IU (equivalent to 3.0 micrograms) of lutropin alfa.

The reconstituted solution contains 150 IU r-hFSH and 75 IU r-hLH per milliliter.

Excipients: 30 mg sucrose, 1.11 mg disodium phosphate dihydrate, 0.45 mg sodium dihydrogen phosphate monohydrate, 0.1 mg methionine, 0.05 mg polysorbate 20. PERGOVERIS also contains phosphoric acid and/or sodium hydroxide used for pH adjustment of the formulated solution.

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

PERGOVERIS solution for injection in a pre-filled pen

PERGOVERIS (follitropin alfa/lutropin alfa injection [150 IU:75 IU]) is a clear, colorless to slightly yellow solution with a pH of 6.5-7.5. The solution is presented in 3 mL colorless glass cartridges [type I borosilicate glass, with a grey bromobutyl rubber plunger stopper and a crimp cap made with grey rubber stopper (latex-free) septum and aluminium] pre-assembled in a pre-filled pen.

Each multidose pre-filled pen contains one of either:

- 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 and can deliver two doses of PERGOVERIS 150 IU/75 IU;
- 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 and can deliver three doses of PERGOVERIS150 IU/75 IU; or
- 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 and can deliver six doses of PERGOVERIS150 IU/75 IU.

The product is supplied in packs of:
- 1 PERGOVERIS 300 IU/150 IU pre-filled pen and 5 injection needles.
- 1 PERGOVERIS 450 IU/225 IU pre-filled pen and 7 injection needles.
- 1 PERGOVERIS 900 IU/450 IU pre-filled pen and 14 injection needles.

Not all pack sizes may be marketed.

Excipients (300 IU/150 IU): sucrose, arginine monohydrochloride, phenol, disodium phosphate dehydrate, sodium dihydrogen phosphate monohydrate, poloxamer 188, methionine, sodium hydroxide (for pH adjustment), phosphoric acid (for pH adjustment).

Excipients (450 IU/225 IU): sucrose, arginine monohydrochloride, phenol, disodium phosphate dehydrate, sodium dihydrogen phosphate monohydrate, poloxamer 188, methionine, sodium hydroxide (for pH adjustment), phosphoric acid (for pH adjustment).

Excipients (900 IU/450 IU): sucrose, arginine monohydrochloride, phenol, disodium phosphate dehydrate, sodium dihydrogen phosphate monohydrate, poloxamer 188, methionine, sodium hydroxide (for pH adjustment), phosphoric acid (for pH adjustment).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: follitropin alfa (150 IU) and lutropin alfa (75 IU)

Chemical name: recombinant human follicle stimulating hormone (r-hFSH)/recombinant human luteinizing hormone (r-hLH)

Molecular formula and molecular mass:

follitropin alfa
Molecular formula: $C_{975}H_{1515}N_{267}O_{305}S_{26}$
Molecular Weight: α-subunit: 14 kDa; β-subunit: 17 kDa

lutropin alfa
Molecular formula: $C_{1014}H_{1609}N_{287}O_{294}S_{27}$
Molecular Weight: α -subunit: 14 kDa; β-subunit: 15 kDa

Structural formula: ***follitropin alfa***

Amino acid sequence of the r-hFSH α-subunit

1	Ala-Pro-Asp-Val-Gln-Asp-Cys-Pro-Glu-Cys
11	Thr-Leu-Gln-Glu-Asn-Pro-Phe-Phe-Ser-Gln
21	Pro-Gly-Ala-Pro-Ile-Leu-Gln-Cys-Met-Gly
31	Cys-Cys-Phe-Ser-Arg-Ala-Tyr-Pro-Thr-Pro
41	Leu-Arg-Ser-Lys-Lys-Thr-Met-Leu-Val-Gln
51	Lys-Asn-Val-Thr-Ser-Glu-Ser-Thr-Cys-Cys
61	Val-Ala-Lys-Ser-Tyr-Asn-Arg-Val-Thr-Val
71	Met-Gly-Gly-Phe-Lys-Val-Glu-Asn-His-Thr
81	Ala-Cys-His-Cys-Ser-Thr-Cys-Tyr-Tyr-His
91	Lys-Ser

Amino acid sequence of the r-hFSH β-subunit

1	Asn-Ser-Cys-Glu-Leu-Thr-Asn-Ile-Thr-Ile
11	Ala-Ile-Glu-Lys-Glu-Glu-Cys-Arg-Phe-Cys
21	Ile-Ser-Ile-Asn-Thr-Thr-Trp-Cys-Ala-Gly
31	Tyr-Cys-Tyr-Thr-Arg-Asp-Leu-Val-Tyr-Lys
41	Asp-Pro-Ala-Arg-Pro-Lys-Ile-Gln-Lys-Thr
51	Cys-Thr-Phe-Lys-Glu-Leu-Val-Tyr-Glu-Thr
61	Val-Arg-Val-Pro-Gly-Cys-Ala-His-His-Ala
71	Asp-Ser-Leu-Tyr-Thr-Tyr-Pro-Val-Ala-Thr

81 Gln-Cys-His-Cys-Gly-Lys-Cys-Asp-Ser-Asp
91 Ser-Thr-Asp-Cys-Thr-Val-Arg-Gly-Leu-Gly
101 Pro-Ser-Tyr-Cys-Ser-Phe-Gly-Glu-Met-Lys
111 Glu

Asn : N-glycosylation site

lutropin alfa

Amino acid sequence of the r-hLH α-subunit

1 Ala-Pro-Asp-Val-Gln-Asp-Cys-Pro-Glu-Cys
11 Thr-Leu-Gln-Glu-Asn-Pro-Phe-Phe-Ser-Gln
21 Pro-Gly-Ala-Pro-Ile-Leu-Gln-Cys-Met-Gly
31 Cys-Cys-Phe-Ser-Arg-Ala-Tyr-Pro-Thr-Pro
41 Leu-Arg-Ser-Lys-Lys-Thr-Met-Leu-Val-Gln
51 Lys-Asn-Val-Thr-Ser-Glu-Ser-Thr-Cys-Cys
61 Val-Ala-Lys-Ser-Tyr-Asn-Arg-Val-Thr-Val
71 Met-Gly-Gly-Phe-Lys-Val-Glu-Asn-His-Thr
81 Ala-Cys-His-Cys-Ser-Thr-Cys-Tyr-Tyr-His
91 Lys-Ser

Amino acid sequence of the r-hLH β-subunit

1 Ser-Arg-Glu-Pro-Leu-Arg-Pro-Trp-Cys-His
11 Pro-Ile-Asn-Ala-Ile-Leu-Ala-Val-Glu-Lys
21 Glu-Gly-Cys-Pro-Val-Cys-Ile-Thr-Val-Asn
31 Thr-Thr-Ile-Cys-Ala-Gly-Tyr-Cys-Pro-Thr
41 Met-Met-Arg-Val-Leu-Gln-Ala-Val-Leu-Pro
51 Pro-Leu-Pro-Gln-Val-Val-Cys-Thr-Tyr-Arg
61 Asp-Val-Arg-Phe-Glu-Ser-Ile-Arg-Leu-Pro
71 Gly-Cys-Pro-Arg-Gly-Val-Asp-Pro-Val-Val
81 Ser-Phe-Pro-Val-Ala-Leu-Ser-Cys-Arg-Cys
91 Gly-Pro-Cys-Arg-Arg-Ser-Thr-Ser-Asp-Cys
101 Gly-Gly-Pro-Lys-Asp-His-Pro-Leu-Thr-Cys
111 Asp-His-Pro-Gln-Leu-Ser-Gly-Leu-Leu-Phe
121 Leu

Asn : N-glycosylation site

Physicochemical properties:

follitropin alfa

The r-hFSH drug substance consists of two non-covalently linked, non-identical protein components designated as the α- and β-subunits. The α-subunit is composed of 92 amino acids carrying

two carbohydrate moieties linked to Asn-52 and Asn-78. The β-subunit is composed of 111 amino acids carrying two carbohydrate moieties linked to Asn-7 and Asn-24. r-hFSH is derived from a Chinese Hamster Ovary cell line which has been modified by the addition of the human genes encoding the FSH α- and β-chains.

lutropin alfa

The r-hLH drug substance is a heterodimeric glycoprotein consisting of two non-covalently linked, non-identical subunits designated as the α- and β-subunits. The α-subunit is composed of 92 amino acids carrying two N-linked carbohydrate moieties at Asn-52 and Asn-78. The β-subunit is composed of 121 amino acids carrying a single N-linked carbohydrate moiety at Asn-30.

CLINICAL TRIALS

Study Demographics and Trial Design

The clinical efficacy of lutropin alfa (LUVERIS) co-administered with follitropin alfa (GONAL-f) has been demonstrated in six clinical studies in 170 women who underwent 285 ovarian stimulation cycles for efficacy analysis. In all studies, the patients were women with hypogonadotropic hypogonadism (HH). Four of the trials included only HH patients with severe LH deficiency (<1.2 IU/mL) and the remaining 2 included a subset of patients with severe LH deficiency. The patients' ages ranged from 20-40 years.

Patients received daily subcutaneous doses of lutropin alfa of 25-225 IU, in addition to daily subcutaneous injections of 75-150 IU GONAL-F (follitropin alfa for injection).

All clinical trials had been completed for the purpose of evaluating the component drug lutropin alfa when given to the hypogonadotropic hypogonadism population in conjunction with follitropin alfa for the purpose of ovarian stimulation. Further information regarding individual trials can be found in the Product Monographs for LUVERIS and GONAL-f.

Of the 148 women in the studies that received a non-zero dose of lutropin alfa, 102 received the 150 IU r-hFSH:75 IU r-hLH dose level for at least one cycle. In about one half of those cycles, the injections were given as a single mixed injection of both component drugs. Of the 170 women enrolled in a trial (including those that received only r-hFSH), 119 were hypogonadotropic hypogonadism patients with severe LH deficiency.

The details of such studies are presented below in Table 4.

Table 4: Summary of Patient Demographics for Clinical Trials in Women with Hypogonadotropic Hypogonadism

Study #	Trial design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (range)
6253[3]	Phase II/III open-label, randomized, dose-finding, comparative, parallel group, multicenter study	Lutropin alfa 0, 25, 75 or 225 IU SC daily, up to 20 days Lutropin alfa 0 IU Lutropin alfa 25 IU Lutropin alfa 75 IU Lutropin alfa 225 IU	 9 8 11 10	28.7 (20-35)
6905[4]	Phase II/III open-label, randomized, dose-finding, comparative, parallel group, multicenter study	Lutropin alfa 0, 25, 75 or 225 IU SC daily, up to 21 days Lutropin alfa 0 IU Lutropin alfa 25 IU Lutropin alfa 75 IU Lutropin alfa 225 IU	 11 9 11 9	30.5 (22-40)

Study #	Trial design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (range)
7798	Phase III randomized, dose-finding, multicenter study	Lutropin alfa 75, 150 or 225 IU SC daily, up to 21 days Lutropin alfa 75 IU Lutropin alfa 150 IU Lutropin alfa 225 IU	 5 5 5	29 (20-34)
8297[5]	Phase III non-comparative, multicenter study	Lutropin alfa 75 IU SC daily, up to 21 days	38	30 (25-40)
21008[6]	Phase III randomized, controlled, double-blind, multicenter study	Lutropin alfa 0 or 75 IU SC daily, up to 14 days	13 26	30 (21-39)
21415[7]	Phase III open-label, non-comparative, multicenter study	Lutropin alfa 75 IU SC daily, up to 14 days	31 (11 LH-naïve continued from Study 21008)	30.5 (21-40)

In all trials, the primary endpoint was follicular development, which was defined as the following:

(i) At least 1 follicle with mean diameter ≥17-18 mm,

(ii) Pre-ovulatory serum E2 ≥109-200 pg/mL, and

(iii) Mid-luteal phase P4 ≥ 7.9-10 ng/mL (25-30nmol/L)

The ranges cited above represent the entirety of the clinical trial programme; criteria varied within these ranges according to trial protocol. Consult the References cited for further details of individual trials.

In some trials, patients at risk of OHSS were included as having successful follicular development despite having hCG withheld or not meeting all the above criteria. This was pre-specified in some of the trials. All trials included the establishment of a pregnancy as a success regardless of meeting the above criteria.

While the risk of OHSS may indicate either an early adverse reaction or successful follicular development, it is not indicative of successful development for the purposes of establishing a pregnancy since hCG trigger would be withheld and cycle cancelled. Because of the differences in interpretation of "risk of OHSS" the results below include both the follicular development success rates with and without that criterion.

Study results

The data from the six studies to the primary efficacy endpoint are shown in Table 5.

Table 5: Primary Endpoint, Follicular Development in Hypogonadotropic Hypogonadism

	Trials 21008, 21415, 6905, 6253, 7798 and 8297				
	Follitropin alfa 150 IU/day plus lutropin alfa daily dose of:				
	0 IU (placebo)	25 IU	75 IU	150 IU	225 IU
Patients	33	17	102*	5	24
Severely LH deficient patients	25	13	57	5	19
# Cycles**	32	16	192	14	31
Follicular development (OHSS risk excluded)	7 (21.9%)	9 (56.2%)	112 (58.3%)	4 (28.6%)	18 (58.1%)
Follicular development (OHSS risk included)	10 (31.2%)	11 (68.8%)	143 (74.5%)	6 (42.9%)	22 (71.0%)

*Includes 11 LH-naïve patients from Study 21008 continuing in Study 21415.

**Studies 6905, 6253 primary efficacy endpoint was assessed only for Cycle A. Studies 7798, 8297, 21008 and 21415 included all cycles for assessment of primary efficacy endpoint.

DETAILED PHARMACOLOGY

Human Pharmacokinetics

The pharmacokinetic interaction between lutropin alfa and follitropin alfa was evaluated in the healthy subjects downregulated with a GnRH agonist (ZOLADEX) by comparing individually administered FSH or LH to fixed dose combination (at 2:1 ratio of FSH vs. LH) of the two agents. The results demonstrated that the PK parameters of $AUC_{0\text{-last}}$, C_{max}, and T_{max} are similar between administered alone for FSH (at dose 300 IU, Study 23718) or LH (at dose 450 IU, Study 23722) and co-administration of the two components at 2:1 ratio (FSH/LH) (see Figures 3 and 4).

Figure 3: Study 23718 Mean FSH Serum Concentration Time Profiles after Subcutaneous Administration of 300 IU r-hFSH as GONAL-f (reference) versus r-hFSH in Fixed Combination with 150 IU of r-hLH (n = 35) (linear scale)

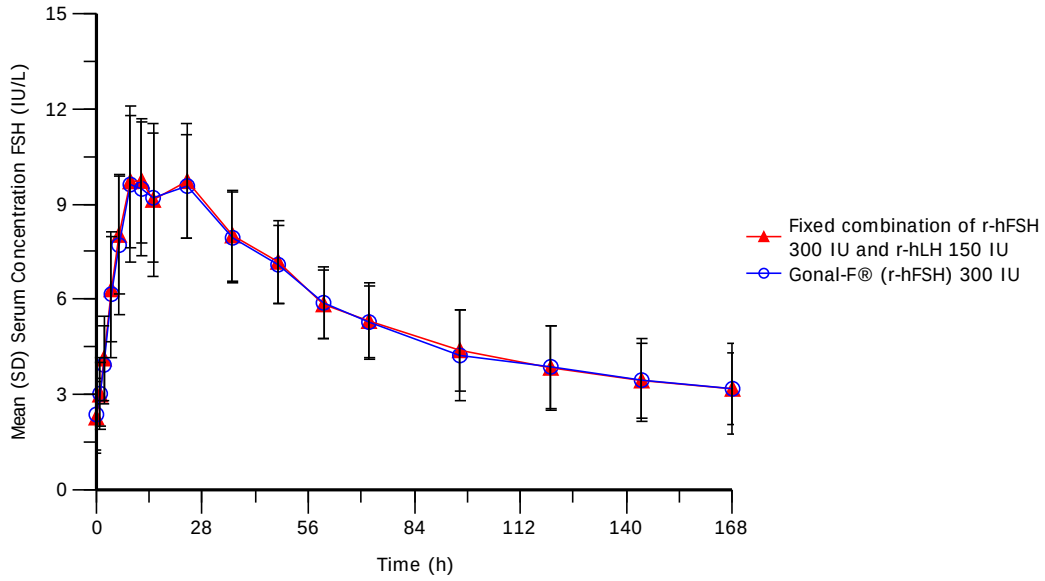
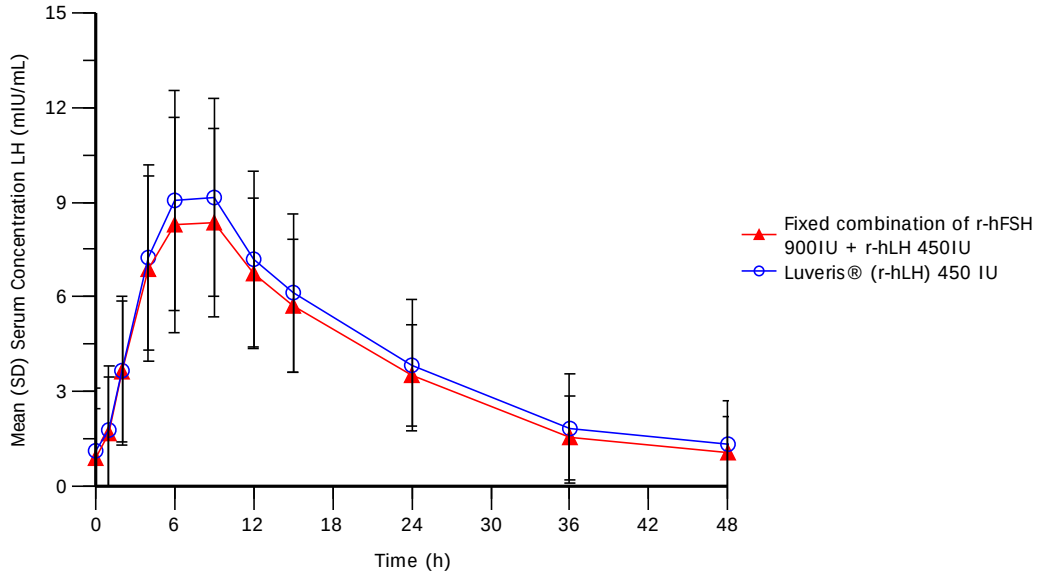


Figure 4: Study 23722 Mean LH Serum Concentration-Time Profiles after Subcutaneous Administration of 450 IU r-hLH as LUVERIS (Reference) versus r-hLH in Fixed combination with 900 IU r-hFSH (linear scale)



Study EMR200031-002 study evaluated the pharmacokinetic (PK) dose-proportionality of r-hFSH after single SC administration of PERGOVERIS (follitropin alfa/lutropin alfa for injection [150 IU:75 IU]) at doses of 300, 450, and 900 IU r-hFSH in pituitary down-regulated healthy premenopausal females. Dose proportionality for FSH was demonstrated based on the results of the statistical analysis of the PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

For additional information on bioequivalence between PERGOVERIS powder for injection and FSH, LH co-administration, pharmacokinetic profiles for FSH and LH, please see PART I: ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, as well as the GONAL-f and LUVERIS prescribing information.

For additional information on bioequivalence between PERGOVERIS powder for injection and PERGOVERIS solution for injection in pre-filled pen, please see PART I: ACTION AND CLINICAL PHARMACOLOGY.

TOXICOLOGY

A local tolerance study in New Zealand White (NZW) rabbits (Study IMP 23595) was performed with PERGOVERIS (follitropin alfa/lutropin alfa for injection [150 IU:75 IU]) powder for injection to assess tolerability after single and repeat dosing at clinically relevant dose/volume and concentration of the combination product (150 IU r-hFSH + 75 IU r-hLH in 1 mL of Water for Injection). There were no notable local reactions seen in the study.

A local tolerance study using the solution for injection formulation of PERGOVERIS (follitropin alfa/lutropin alfa injection [150 IU:75 IU]) was performed in NZW rabbits to assess tolerability after single and repeat dosing at clinically relevant doses/volumes (expected in clinical use or adopted in the bioequivalence study in healthy female volunteers, Study EMR200061-006). PERGOVERIS liquid formulation did not induce test item-related alterations at the injection sites.

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PART III: CONSUMER INFORMATION

PrPERGOVERIS®
follitropin alfa/lutropin alfa for injection (150 IU:75 IU)
Powder and diluent for injection

This leaflet is part III of a three-part "Product Monograph" published when PERGOVERIS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PERGOVERIS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What is PERGOVERIS?

PERGOVERIS is a combination of GONAL-f and LUVERIS at a fixed dose of 150 IU FSH and 75 IU LH. Prior to therapy with PERGOVERIS, patients should be informed of the duration of treatment and need for monitoring.

What the medication is used for:
PERGOVERIS is indicated for the stimulation of follicular development in hypogonadotropic hypogonadal women with severe LH deficiency (LH< 1.2 IU/L) and FSH deficiency (≤ 5.0 IU/L) who are candidates for concurrent therapy with FSH and LH.

The medicinal product should only be used under the strict supervision of a doctor.

What it does:
Women with hypogonadotropic hypogonadism have pituitary glands that do not release follicle stimulating hormone (FSH) or luteinizing hormone (LH). This means that the follicles are unable to develop and mature, so ovulation cannot take place.

PERGOVERIS contains FSH and LH and is used to stimulate follicular growth for ovulation.

When it should not be used:
Do not use PERGOVERIS if you have:

- Hypersensitivity to the active substances follitropin alfa and lutropin alfa or to any of the excipients or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph
- Primary ovarian failure or anovulation with normal levels of LH and FSH
- Uncontrolled thyroid or adrenal dysfunction
- Tumours of the hypothalamus or pituitary gland
- Ovarian enlargement or cyst of undetermined origin
- Gynecological hemorrhages of undetermined origin
- Sex hormone dependent tumors of the reproductive tract and accessory organs
- Current pregnancy or lactation

The medicine should not be used when a condition exists which would make a normal pregnancy impossible, such as:
- premature menopause,
- malformation of reproductive organs,
- specific tumours of the uterus, including severe uterine fibroids.

What the medicinal ingredients are:
PERGOVERIS is fixed dose combination of 150 IU follitropin alfa (GONAL-f) and 75 IU lutropin alfa (LUVERIS). These hormones belong to the gonadotropin family and are made in laboratories by special recombinant DNA techniques.

What the important nonmedicinal ingredients are:
Sucrose, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, methionine, polysorbate 20, concentrated phosphoric acid and sodium hydroxide.

The diluent is Water for Injection.

For a full listing of nonmedicinal ingredients see Part 1 of the Product Monograph.

What dosage forms it comes in:
PERGOVERIS comes as a powder and diluent for solution for injection.

The powder is a white lyophilized pellet.

The diluent is a clear colourless solution.

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

One vial of powder contains 150 IU of follitropin alfa and 75 IU of lutropin alfa. One vial of diluent contains 1 ml of Water for Injection.

PERGOVERIS is also available in a pre-filled, multidose pen (see Product Monograph for information).

WARNINGS AND PRECAUTIONS

BEFORE YOU USE PERGOVERIS:

If you have porphyria, which is a group of inherited disorders (a disorder that may be passed on from parents to children), you should inform your doctor as the use of certain medications may trigger an attack of the illness. If you notice your skin becoming fragile and blisters easily (especially areas that are frequently exposed to sunlight) and/or you have stomach or limb pain you should tell your doctor who may recommend that you stop treatment.

This treatment increases your risk of developing ovarian hyperstimulation syndrome (OHSS) (see Section SIDE EFFECTS). PERGOVERIS treatment seldom gives rise to significant OHSS unless the medicine used to induce final follicular maturation (containing human chorionic gonadotropin - hCG) is administered. It is therefore prudent to withhold administration of hCG in cases where OHSS is developing and not to have sexual intercourse. You should use barrier methods for at least four days.

If you are at risk of thromboembolic events (formation of a blood clot in vein or artery), because of your personal or family history, treatment with gonadotropins, like pregnancy itself, may further increase the risk. If you think you may have such a risk, please talk to your doctor.

In patients undergoing induction of ovulation, the incidence of a multiple pregnancy and births is increased compared with natural conception.

The frequency of miscarriages is higher than in the normal population, but similar to the rate found overall in women with fertility problems.

Women with a history of tubal disease are at a risk of ectopic pregnancy (pregnancy where the embryo is implanted outside the womb), whether the pregnancy is obtained by spontaneous conception or with fertility treatments.

There have been reports of tumours of the ovary and other reproductive organs, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment.

There have been isolated reports of non-serious allergic reactions to PERGOVERIS. If you had this type of reaction to similar medicines, inform your doctor.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

PERGOVERIS should not be administered as a mixture with other medicinal products in the same injection, except for follitropin alfa, if prescribed by your doctor. PERGOVERIS may be mixed in the same syringe with follitropin alfa and given in one injection.

PROPER USE OF THIS MEDICATION

Usual dose:
Always take PERGOVERIS exactly as your doctor or Healthcare Professional (HCP) has instructed you. You should check with your doctor or HCP if you are not sure. With professional guidance, you can learn to inject yourself, in the comfort and privacy of your own home.

It is recommended that you inject PERGOVERIS at around the same time each day.

The usual dose is one vial of PERGOVERIS taken every day for up to three weeks. According to your response, your doctor may increase your dose of follitropin alfa usually by 37.5-75 IU at 7 to 14-day intervals.

When the desired response has been obtained, a single injection of hCG is given 24-48 hours after the last injection of PERGOVERIS. It is recommended that you have sexual intercourse on the day of, and the day following administration of the hCG. Alternatively, intrauterine insemination (IUI) or *in vitro* fertilization (IVF) may be performed.

If an excessive response occurs, treatment should be stopped and hCG withheld (see section SIDE EFFECTS). For the following cycle, your doctor may prescribe follitropin alfa at a lower dose than that used in the previous cycle.

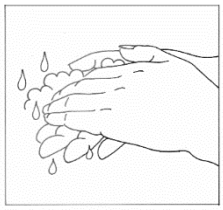
Every treatment is individualized. Yours has been carefully designed for you by your doctor according to your own specific needs. It is very important that you keep your appointments and follow your doctor's instructions, particularly with regard to the amount and frequency of the medication you are taking.

Route of administration

PERGOVERIS is intended for subcutaneous use that means given by injection just under the skin. Each vial is intended for a single use only.

If you self-administer PERGOVERIS, please read the following instructions carefully:

- 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:

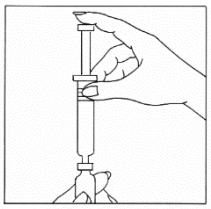
    - one vial containing PERGOVERIS (powder) (or as instructed by your doctor)
    - one vial of diluent (liquid)
    - three alcohol swabs
    - one syringe
    - one needle for mixing (long)
    - one fine bore needle for subcutaneous injection (short)
    - sharps container (which may be provided by your clinic or pharmacist)

DRAWING UP THE DILUENT FROM THE VIAL

Remove the protective cap from the vial containing the diluent. Use an alcohol swab to clean the rubber stopper and metal ring. Discard the alcohol swab.

Remove the syringe from its package and carefully remove the cap off of the long mixing needle, taking care not to let the needle touch any surface. Pull the plunger back until it is at the line next to the number showing the amount of diluent that you need to draw up as advised by your healthcare provider (for example: 1 cc).

Place the vial of diluent on a clean, flat surface. Push the needle through the center of the rubber stopper on the vial. Then, push the plunger all the way in.



Keeping the needle in the vial, lift the vial and turn it upside down. Check to see that the needle tip is in the liquid. Be sure you completely cover the needle tip with liquid before pulling back on the plunger. Slowly pull the plunger back until you see the required amount of diluent in the syringe. Discard the vial containing any unused diluent into a sharps container. Carefully replace the cap on the needle and place the syringe on a clean surface.

MIXING THE MEDICATION FOR INJECTION

Remove the protective cap from the PERGOVERIS powder vial. Use an alcohol swab to clean the rubber stopper and metal ring. Discard the alcohol swab.

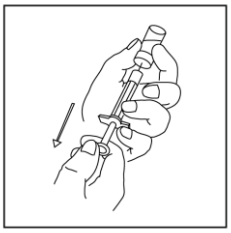
Pick up the syringe containing the diluent and carefully remove the cap. Push the needle through the center of the rubber stopper on the PERGOVERIS powder vial. Slowly inject the diluent into the powder vial by pushing down on the plunger.

Leaving the needle in the vial, gently rotate the vial between your fingers until all of the powder is dissolved. Do not shake. Check that the solution is clear and colorless. Do not use if the solution is cloudy, discolored, or contains particles.

DRAW UP THE MEDICATION

After the powder has dissolved, turn the vial upside down, and gently draw up the entire contents of the vial into the syringe, being careful not to pull the plunger out of the syringe. It may help to slowly tip the vial.

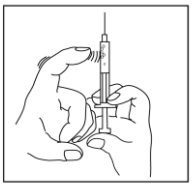
Be sure you completely cover the needle tip with liquid before you pull back the plunger.



CHANGE THE NEEDLE

Hold the syringe with the needle pointing upwards. Create a small airspace at the top of the barrel by gently pulling the plunger back. Carefully recap the needle, then twist and remove the mixing needle. Replace the long mixing needle with the fine-bore, short needle for injection. Twist to attach, and pull to remove the cap.

Hold the syringe with the needle pointing upwards and gently flick the syringe so that, if there are any large air bubbles, they will rise to the top.



If large air bubbles are present, gently push the plunger upwards until a small droplet of liquid appears at the tip of the needle. Replace the cap on the needle. Place the syringe on a clean surface.

Do not worry if you are unable to remove very tiny bubbles; they will do you no harm.

PREPARE THE INJECTION SITE

Select the site of injection (e.g. top of thigh, tummy). Choose a different site each day. Wipe the chosen area with an alcohol swab, cleansing an area of approximately 5 cm x 5 cm (an area about the size of a tea bag). Lay the used side of the swab next to your working surface or on the alcohol swab wrapper.

INJECTING THE MEDICATION

Pick up the syringe and remove the cap from the needle. Using the hand with which you write, hold the syringe like a pencil or as if "throwing a dart". With your other hand, gently squeeze the skin together to make a little elevation at the injection site. Using a "dart like motion", insert the needle at a 90° angle. (You need very little force but quick action).

Inject the solution by gently pushing on the plunger with your index finger. Take as much time as you need to inject all the solution. As you release the skin from your grip, withdraw the needle by pulling it straight out. Clean the skin with the clean side of the alcohol swab using a circular motion. If there is minor oozing you may need to apply a small amount of pressure.

DISPOSE OF ALL USED ITEMS

Once you have finished your injection, immediately discard the needles and syringe (without recapping the needle) into the disposal container.

Overdose:
The effects of an overdose of PERGOVERIS are unknown, nevertheless one might expect ovarian hyperstimulation syndrome to occur, which is further described in section SIDE EFFECTS. However this will only occur if hCG is administered.

If you have accidentally injected too much PERGOVERIS, contact your physician, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you missed a dose of PERGOVERIS, do not take a double dose, please contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, PERGOVERIS may cause side effects, although not everyone gets them.

The most commonly reported side effects are abdominal pain, pelvic pain, breast pain, constipation, dysmenorrhea (painful menstruation), flatulence (stomach or intestinal gas), headache, nausea, and local reactions at the injection site (pain, redness, itching, bruising, swelling and/or irritation).

When taking PERGOVERIS, there is a risk of developing ovarian hyperstimulation syndrome (OHSS). The early warning signs of development of OHSS are severe abdominal pain, nausea, vomiting and weight gain. Since OHSS develops rapidly, if you experience any of these symptoms, contact your doctor immediately.

In serious, but rare cases, ovarian hyperstimulation syndrome with clearly enlarged ovaries can include accumulation of fluid in the abdomen or thorax as well as

more serious thromboembolic (abnormal blood clotting) complications. In rare cases, thromboembolic complications can also be found independently of ovarian hyperstimulation syndrome.

In view of the above, to prevent such events, when the ovarian response is excessive, treatment with PERGOVERIS should be discontinued by your doctor and treatment with hCG abandoned.

Isolated cases of non-serious allergic reactions to PERGOVERIS have been reported.

Ectopic pregnancy (embryo implanted outside the uterus) may occur especially in women with a history of prior disease/scarring in their Fallopian tubes.

If you experience serious side effects or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking PERGOVERIS, contact your doctor or pharmacist.

HOW TO STORE IT

Do not store above 25°C. Avoid freezing. Store in the original package in order to protect from light.

Keep out of the reach of children.

Do not use PERGOVERIS after the expiry date which is stated on the vial after EXP. The expiry date refers to the last day of that month.

Do not use PERGOVERIS if you notice any visible signs of deterioration.

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

The medicine must be administered immediately after reconstitution.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health care professionals can be obtained by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php), http://www.emdserono.ca, or by calling EMD Serono at 1-800-387-8479.

This leaflet was prepared by EMD Serono, A Division of EMD Inc., Canada

Last revised:

PART III: CONSUMER INFORMATION

PrPERGOVERIS®
follitropin alfa/lutropin alfa injection (150 IU:75 IU)
Solution for Injection in a Pre-filled Pen

This information is part III of a three-part "Product Monograph" published when PERGOVERIS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PERGOVERIS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What is PERGOVERIS?
PERGOVERIS is a combination of GONAL-f and LUVERIS at a fixed dose of 150 IU FSH and 75 IU LH. Prior to therapy with PERGOVERIS, patients should be informed of the duration of treatment and need for monitoring.

What is the medication used for:
PERGOVERIS is indicated for the stimulation of follicular development in hypogonadotropic hypogonadal women with severe LH deficiency (LH< 1.2 IU/L) and FSH deficiency (≤ 5.0 IU/L) who are candidates for concurrent therapy with FSH and LH.

The medicinal product should only be used under the strict supervision of a doctor.

What it does:
Women with hypogonadotropic hypogonadism have pituitary glands that do not release follicle stimulating hormone (FSH) or luteinizing hormone (LH). This means that the follicles are unable to develop and mature, so ovulation cannot take place.

PERGOVERIS contains FSH and LH and is used to stimulate follicular growth for ovulation.

When it should not be used:
Do not use PERGOVERIS if you have:

- Hypersensitivity to the active substances follitropin alfa and lutropin alfa or to any of the excipients or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph
- Primary ovarian failure or anovulation with normal levels of LH and FSH
- Uncontrolled thyroid or adrenal dysfunction
- Tumours of the hypothalamus or pituitary gland
- Ovarian enlargement or cyst of undetermined origin
- Gynecological hemorrhages of undetermined origin
- Sex hormone dependent tumors of the reproductive tract and accessory organs
- Current pregnancy or lactation

PERGOVERIS should not be used when a condition exists which would make a normal pregnancy impossible, such as:

- premature menopause,
- malformation of reproductive organs,
- specific tumours of the uterus, including severe uterine fibroids.

What the medicinal ingredients are:
PERGOVERIS is fixed dose combination of 150 IU follitropin alfa (GONAL-f) and 75 IU lutropin alfa (LUVERIS). These hormones belong to the gonadotropin family and are made in laboratories by special recombinant DNA techniques.

What the important nonmedicinal ingredients are:
Sucrose, arginine monohydrochloride, phenol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, poloxamer 188, methionine, phosphoric acid and sodium hydroxide for pH adjustment

For a full listing of nonmedicinal ingredients see Part 1 of the Product Monograph.

What dosage forms it comes in:
PERGOVERIS is a clear, colorless to slightly yellow solution for injection available in pre-filled pens that can deliver 2 doses, 3 doses or 6 doses of 150 IU follitropin alfa and 75 IU lutropin alfa. Not all pack sizes may be marketed.

PERGOVERIS also comes as a powder and diluent for solution for injection (see Product Monograph for information)

WARNINGS AND PRECAUTIONS

BEFORE YOU USE PERGOVERIS:

If you have porphyria, which is a group of inherited disorders (a disorder that may be passed on from parents to children), you should inform your doctor as the use of certain medications may trigger an attack of the illness. If you notice your skin becoming fragile and blisters easily (especially areas that are frequently exposed to sunlight)

and/or you have stomach or limb pain you should tell your doctor who may recommend that you stop treatment.

This treatment increases your risk of developing ovarian hyperstimulation syndrome (OHSS) (see Section SIDE EFFECTS). PERGOVERIS treatment seldom gives rise to significant OHSS unless the medicine used to induce final follicular maturation (containing human chorionic gonadotropin - hCG) is administered. It is therefore prudent to withhold administration of hCG in cases where OHSS is developing and not to have sexual intercourse. You should use barrier methods for at least four days.

If you are at risk of thromboembolic events (formation of a blood clot in vein or artery), because of your personal or family history, treatment with gonadotropins, like pregnancy itself, may further increase the risk. If you think you may have such a risk, please talk to your doctor.
In patients undergoing induction of ovulation, the incidence of a multiple pregnancy and births is increased compared with natural conception.

The frequency of miscarriages is higher than in the normal population, but similar to the rate found overall in women with fertility problems.

Women with a history of tubal disease are at a risk of ectopic pregnancy (pregnancy where the embryo is implanted outside the womb), whether the pregnancy is obtained by spontaneous conception or with fertility treatments.

There have been reports of tumours of the ovary and other reproductive organs, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment.

There have been isolated reports of non-serious allergic reactions to PERGOVERIS. If you had this type of reaction to similar medicines, inform your doctor.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

PERGOVERIS should not be administered as a mixture with other medicinal products in the same injection, but may be given at the same time as follitropin alfa in a separate injection, if prescribed by your doctor.

PROPER USE OF THIS MEDICATION

Usual dose:
Always take PERGOVERIS exactly as your doctor or Healthcare Professional (HCP) has instructed you. You should check with your doctor or HCP if you are not sure. With professional guidance, you can learn to inject yourself, in the comfort and privacy of your own home.

It is recommended that you inject PERGOVERIS at around the same time each day.

A treatment regimen commences with the recommended dose of PERGOVERIS containing 150 IU follitropin alfa and 75 IU lutropin alfa. This is one dose from your pre-filled pen. According to your response, your doctor may increase your dose of follitropin alfa usually by 37.5-75 IU at 7 to 14-day intervals.

When the desired response has been obtained, a single injection of hCG is given 24-48 hours after the last injection of PERGOVERIS. It is recommended that you have sexual intercourse on the day of, and the day following administration of the hCG. Alternatively, intrauterine insemination (IUI) or *in vitro* fertilization (IVF) may be performed.

If an excessive response occurs, treatment should be stopped and hCG withheld (see section SIDE EFFECTS). For the following cycle, your doctor may prescribe follitropin alfa at a lower dose than that used in the previous cycle.

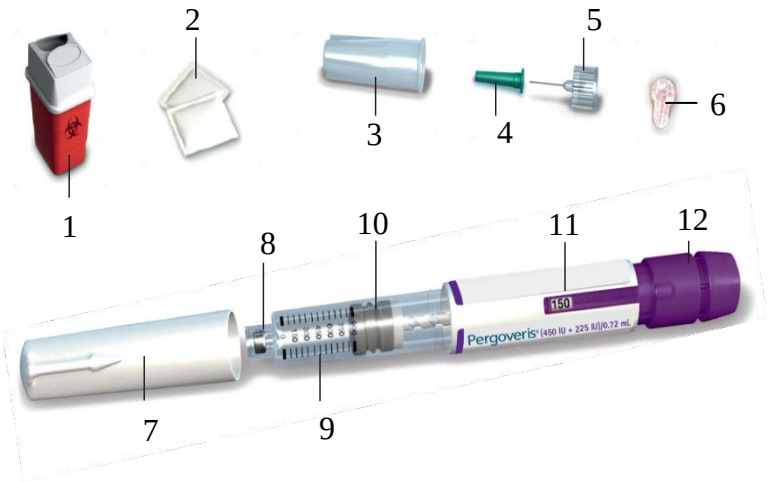
Every treatment is individualized. Yours has been carefully designed for you by your doctor according to your own specific needs. It is very important that you keep your appointments and follow your doctor's instructions, particularly with regard to the amount and frequency of the medication you are taking.

Route of administration

PERGOVERIS is intended for subcutaneous use that means given by injection just under the skin.

If you self-administer PERGOVERIS, please read the following instructions carefully:

PERGOVERIS Pre-filled Pen and other materials you may need for injection.



1. Sharps disposal container
2. Alcohol swabs
3. Outer needle cap
4. Inner needle shield
5. Removable needle
6. Peel-off seal tab
7. Pen cap
8. Threaded needle connector
9. Reservoir holder
10. Plunger piston
11. Dose Display
12. Dose setting knob

1. Before you start using PERGOVERIS pre-filled pen:

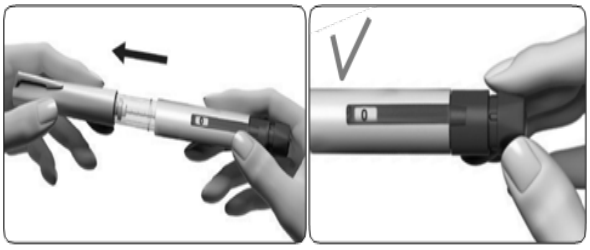
- Wash your hands with soap and water. It is important that your hands and items you use be as clean as possible.

- On a clean surface, e.g., clean table or kitchen surface, lay out everything you will need:
  - PERGOVERIS pre-filled pen
  - One removable injection needle
  - Alcohol swabs
  - Sharps disposal container

- Verify the **expiration date** on the label. Do not use expired medication.

2. Getting your PERGOVERIS pen ready for injection

- Take off the pen cap.
- Wipe the end of the threaded tip (containing the rubber centre) using an alcohol swab.
- Verify that the Dose Display is set to "0". The numbers in the dose feedback window represent the number of International Units or IU and show the dose of follitropin alfa. Your doctor will tell you how many IUs of follitropin alfa to inject each day.

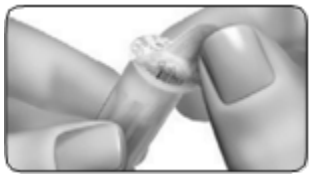


- Prepare your needle for injection:
  - Get a new needle – only use the "single-use" needles supplied
  - Hold the outer needle cap firmly
  - Check that the peel-off seal on the outer needle cap is not damaged or loose:

Example of a good seal

Example of a bad seal

- Remove the peel-off seal



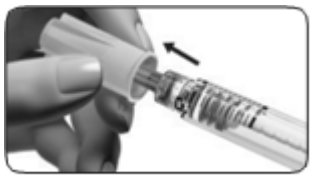
CAUTION: If the peel-off seal is damaged or loose, do not use the needle. Throw it away in a sharps disposal container. Get a new needle.

3. Attach the needle

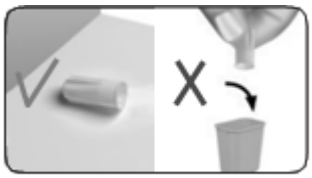
- Screw the threaded tip of the PERGOVERIS pen into the outer needle cap until you feel a light resistance.

  - Important Note: Do not attach the needle too tightly; the needle could be difficult to remove after the injection.

- Remove the outer needle cap by pulling it gently. Put it aside for later use.



- Do not throw away the outer needle cap; you will need it for removing the needle from the pen.

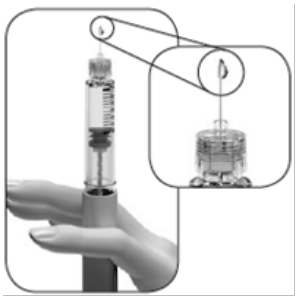


- Hold the PERGOVERIS pen with the needle pointing upwards.

- **Please note: if this is NOT a brand new PERGOVERIS pen (you have done previous injections with this pen), then proceed to Section 4: "Setting the dose prescribed by your doctor".**
  - Carefully remove the green inner shield by pulling it straight off and discard it.
    - Warning: Do not recap the needle with the green inner shield as this can lead to needle stick.

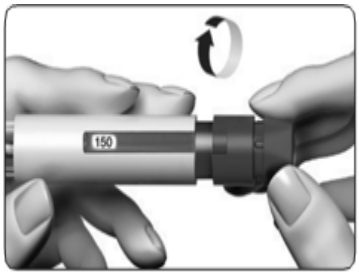
- **If this IS A BRAND NEW PEN that you are using for the first time**, look closely at the tip of the needle for a tiny drop of fluid.
  - If you see a tiny drop(s) of fluid, proceed to Section 4 "Setting the dose prescribed by your doctor".
  - If you do not see a tiny drop(s), please see to Section 7 "Preparing your new PERGOVERIS Pre-filled Pen for first time use".

- **Important Note: Only check for drop(s) with a brand new pen. This step is not required if you are doing additional injections using the same pen.**



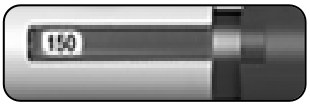
4. Setting the dose prescribed by your doctor

- Turn the dose setting knob forward (or clockwise) until your prescribed dose shows in the Dose Display. Do not push or pull the dose setting knob while you turn it.
  - In this example below, it is 150 IU.



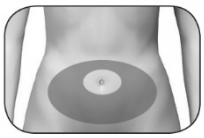
  - If you have turned the knob past your prescribed dose, turn the knob backwards (or counter-clockwise) to correct the dose.

- Important Note: Check that the Dose Display shows your prescribed dose before you move on to the next step.



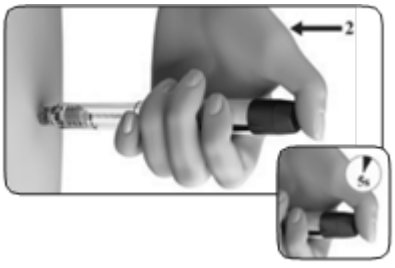
5. Injecting the dose

- Choose an injection site in the area your doctor or nurse has told you to give the injection.
  - Note: To minimize skin irritation, select a different injection site each day.

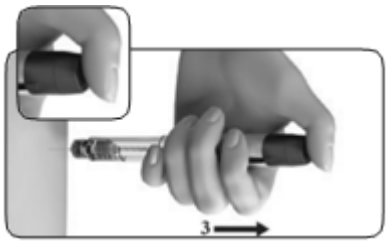


- Clean the skin by wiping the area with an alcohol swab. Allow the site to dry.
- Set the alcohol wipe to the side.
- Verify once more that the Dose Display is showing the correct dose. If it is not the correct dose, you must adjust it by turning the dose setting knob either clockwise or counter-clockwise (see Step 4 "Setting your dose prescribed by your doctor").
- Inject the dose as you were trained to do by your doctor or nurse
  - Holding the pen in one hand, use your other hand to gently squeeze the skin together to make a raised area at the injection site.
  - Insert the needle at a 90^{o} angle into the skin. You might bend the needle if you do not insert it at a 90^{o} angle.
  - Press the dose knob down as far as it will go and hold it to complete the full injection.

- Hold the dose knob down for a minimum of 5 seconds to ensure you inject the full dose. The larger the dose, the longer it will take to inject.



- **Do not release the dose setting knob until you remove the needle from your skin.**



- Remove the needle from your skin, release the dose setting knob.
- The dose number shown in the Dose Display will turn back to 0 to indicate that the complete dose was delivered. If you see a number higher than 0, proceed to Section 6 "After the Injection – Complete a Partial Injection" (only when needed).

6. After the injection

- Verify you have given a complete injection.
- Check that the dose Display shows 0.

Important Note: If the Dose Display shows a number higher than 0, the PERGOVERIS pen is empty and you have not received your full prescribed dose.

Complete a Partial Injection (only when needed):

- The Dose Display will indicate the missing amount (in the example below, it is 50 IU), you need to inject using a new pen.

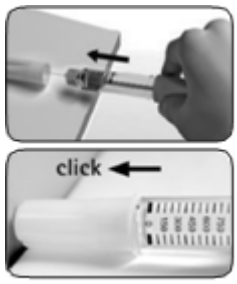
- Repeat Section 1 "Before you start using PERGOVERIS" through Section 2 "Getting your PERGOVERIS pen ready for injection" with a second pen.

- **For a brand new pen that you are using for the first time**, look closely at the tip of the needle for a tiny drop of fluid.
  - If you see a tiny drop(s) of fluid, proceed to Section 4 "Setting the dose prescribed by your doctor".
  - If you do not see a tiny drop(s), please see Section 7 "Preparing your new PERGOVERIS pen for first time use".
- Once your pen is ready, set the dose as described in Section 4 to the missing amount indicated in the Dose Display on your previous pen. Complete your prescribed dose by following steps outlined in Section 5 "Injecting the dose".

  Important Note: Always make sure to use a new needle for each injection.

Removing the needle after each injection:

- Place the outer needle cap on a flat surface.
- Hold the PERGOVERIS pen firmly with one hand, and slip the needle into the outer needle cap. Be careful not to prick yourself with the needle.
- Continue by pushing the capped needle against a firm surface until you hear a "click."

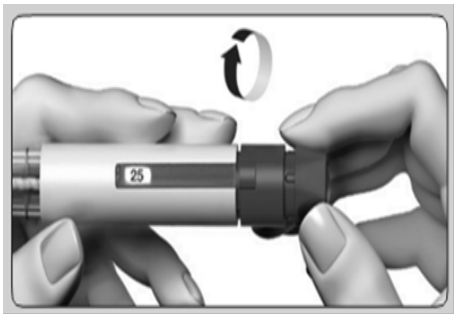


- Grip the outer needle cap and unscrew the needle by turning counter clockwise. Dispose of the used needle safely.

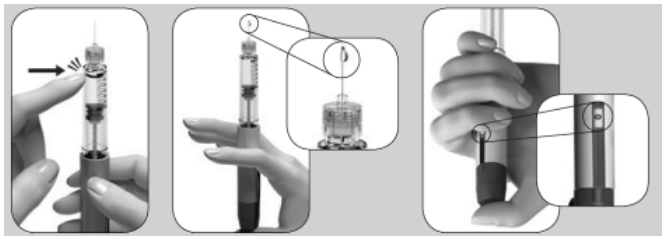
- Never reuse any used needle. Never share needles.
- Recap the pen.

7. Preparing your new PERGOVERIS pen for first time use

- If you do not see a tiny drop(s) at or near the needle tip the first time you use a new pen, you must perform the steps below:
  - Gently turn the dose setting knob clockwise until it reads 25 in the Dose Display. You can turn the dose knob backwards if you turn it past 25.



- Hold the pen with the needle pointing upward.
- Tap the reservoir holder gently.
- Press the dose setting knob as far as it will go. A tiny drop of fluid will appear at the tip of the needle. The amount of fluid seen at the needle tip is part of the overfill from the pre-filled pen.
- Verify that the Dose Display reads "0".



- You may need to repeat this step if you do not see a tiny drop of liquid appearing at the tip of the needle.
- Proceed to Section 4 "Setting the dose prescribed by your doctor".

Storing the PERGOVERIS pen:

CAUTION: Never store the pen with the needle attached. Always remove the needle from the PERGOVERIS pen before replacing the pen cap.

- Store the pen in its original packaging in a safe place
- When the pen is empty, ask your pharmacist how to dispose of it.

Important Note: Medicine should not be disposed of via wastewater or household waste.

Overdose:
The effects of an overdose of PERGOVERIS are unknown, nevertheless one might expect ovarian hyperstimulation syndrome to occur, which is further described in section SIDE EFFECTS. However this will only occur if hCG is administered.

If you have accidentally injected too much PERGOVERIS, contact your physician, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you missed a dose of PERGOVERIS, do not take a double dose, please contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, PERGOVERIS may cause side effects, although not everyone gets them.

The most commonly reported side effects are abdominal pain, pelvic pain, breast pain, constipation, dysmenorrhea (painful menstruation), flatulence (stomach or intestinal gas), headache, nausea, and local reactions at the injection site (pain, redness, itching, bruising, swelling and/or irritation).

When taking PERGOVERIS, there is a risk of developing ovarian hyperstimulation syndrome (OHSS). The early warning signs of development of OHSS are severe abdominal pain, nausea, vomiting and weight gain. Since OHSS develops rapidly, if you experience any of these symptoms, contact your doctor immediately.

In serious, but rare cases, ovarian hyperstimulation syndrome with clearly enlarged ovaries can include accumulation of fluid in the abdomen or thorax as well as more serious thromboembolic (abnormal blood clotting) complications. In rare cases, thromboembolic complications can also be found independently of ovarian hyperstimulation syndrome.

In view of the above, to prevent such events, when the ovarian response is excessive, treatment with

PERGOVERIS should be discontinued by your doctor and treatment with hCG abandoned.

Isolated cases of non-serious allergic reactions to PERGOVERIS have been reported.

Ectopic pregnancy (embryo implanted outside the uterus) may occur especially in women with a history of prior disease/scarring in their Fallopian tubes.

If you experience serious side effects or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking PERGOVERIS, contact your doctor or pharmacist.

HOW TO STORE IT

Store in a refrigerator (2°-8°C). Avoid freezing. Store in the original package in order to protect from light.

Once opened, the pre-filled pen may be stored for a maximum of 28 days outside of the refrigerator (at or below 25°C).

Never store the pen with the needle still attached. Always remove the needle from the PERGOVERIS pre-filled pen before replacing the pen cap. Dispose of the used needles safely.

Keep out of the reach of children.

Do not use PERGOVERIS after the expiry date which is stated on the pen after EXP. The expiry date refers to the last day of that month.

Do not use PERGOVERIS if you notice any visible signs of deterioration, if the liquid contains particles or is not clear.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Report Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at: www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full Product Monograph, prepared for health care professionals can be obtained by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php), http://www.emdserono.ca, or by calling EMD Serono at 1-800-387-8479.

This leaflet was prepared by EMD Serono, A Division of EMD Inc., Canada

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