
PERGOVERIS® 150 IU/75 IU
Follitropin alfa (rch)/Lutropin alfa (rch)

NAME OF MEDICINE

PERGOVERIS contains follitropin alfa (rch) and lutropin alfa (rch).

Recombinant-hFSH is a human gonadotropin hormone of 203 amino acids which consists of two non-covalently linked, non-identical protein components designated as the α - and β -subunits. The α -subunit is common to all four members of a gonadotropin hormone family. The α -subunit is formed by 92 amino acids and possesses two sites of N-linked glycosylation (Asn 52 and Asn 78). Five disulphide bonds contribute to its tertiary structure. The β -subunit is formed by 111 amino acids carrying two carbohydrate moieties linked to Asn-7 and Asn-24 and containing six disulphide bonds.

Recombinant-hLH is a human gonadotropin hormone, composed of two non-covalently linked non-identical subunits, designated α and β . The α -subunit is identical to the one described above. The β -subunit, which is hormone specific, is 121 amino acids in length and possesses a single site of N-linked glycosylation (Asn 30). It contains six disulphide bridges.

CAS-146479-72-3 (follitropin alfa, (rch)).

CAS-152923-57-4 (lutropin alfa); CAS-56832-30-5 (α subunit, lutropin alfa); CAS-53664-53-2 (β subunit, lutropin alfa)

PRESENTATION

PERGOVERIS is supplied in packs of 1, 3 or 10 vials with the corresponding number of vials of solvent. Each vial of PERGOVERIS contains 150 IU (equivalent to 10.92 microgram) of follitropin alfa and 75 IU of lutropin alfa (equivalent to 3.0 microgram) as lyophilised powder, and as excipients sucrose (30 mg), sodium phosphate-dibasic dihydrate (1.11 mg), methionine (0.1 mg), sodium phosphate-monobasic monohydrate (0.45 mg), polysorbate 20 (0.05 mg), phosphoric acid and sodium hydroxide for pH adjustment. Each vial of solvent contains 1 mL Water for Injections.

USES

Actions

Luteinising hormone binds on the ovarian theca (and granulosa) cells and testicular Leydig cells to a receptor shared with human chorionic gonadotrophin hormone (hCG). This LH/hCG transmembrane receptor is a member of the super-family of G protein-coupled receptors; specifically, it has a large extracellular domain. The *in vitro* binding affinities of recombinant hLH, pituitary hLH and hCG to the LH/hCG receptor on murine Leydig tumour cells are of similar orders of magnitude.

In the ovaries, during the follicular phase, LH stimulates the theca cells to secrete androgens, which will be used as the substrate by granulosa cell aromatase enzyme to produce oestradiol, supporting follicle stimulating hormone (FSH)-induced follicular development. At mid-cycle, high levels of LH trigger corpus luteum formation and ovulation. After ovulation, LH stimulates progesterone production in the corpus luteum by increasing the conversion of cholesterol to pregnenolone.

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 oestradiol secretion by the follicles, the growth of which is stimulated by r-hFSH.

In clinical trials the efficacy of the combination of follitropin alfa and lutropin alfa has been demonstrated in women with hypogonadotropic hypogonadism.

In clinical trials (studies 6253 and 21008), patients 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 achievement of an adequate follicular development (which is the optimal well-established, surrogate marker of conception) and considering the risk of ovarian hyperstimulation syndrome (OHSS) versus pregnancy as a success, was consistently found in 66.7% of patients (with LH < 1.2 IU) treated with 150 IU follitropin alfa and 75 IU lutropin alfa (NOTE: this is based on studies 6253 [66.7%] and 21008 [66.7%]). When patients with risk of OHSS were not included in the analysis, adequate follicular development was found in 43.2% of patients (combined analysis of follicular development in studies 6253 and 21008).

Pharmacokinetics

Follitropin alfa and lutropin alfa combination has shown the same pharmacokinetic profile as follitropin alfa and lutropin alfa separately.

Follitropin alfa

Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life around 2 hours and eliminated from the body with a terminal half-life of about 1 day. The steady state volume of distribution and total clearance are 10 L (0.17 L/kg) and 0.6 L/h (0.01 L/h/kg), respectively. One-eighth of the follitropin alfa dose is excreted in the urine.

Following subcutaneous administration, the absolute bioavailability is about 70%. Following repeated administration, follitropin alfa accumulates 3-fold at steady state within 3-4 days. In women whose endogenous gonadotrophin secretion is suppressed, follitropin alfa has nevertheless been shown to effectively stimulate follicular development and steroidogenesis, despite unmeasurable LH levels.

Lutropin alfa

The pharmacokinetics of lutropin alfa have been studied in pituitary desensitised female volunteers from 75 IU up to 40,000 IU.

The pharmacokinetic profile of lutropin alfa is similar to that of urinary-derived hLH. 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 10-12 hours. The steady state volume of distribution is around 10-14 L. Lutropin alfa shows linear pharmacokinetics, as assessed by AUC, which is directly proportional to the dose administered. Total clearance is around 2 L/h, and less than 5% of the dose is excreted in the urine. The mean residence time is approximately 5 hours.

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

INDICATIONS

PERGOVERIS is indicated for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials, these patients were defined by an endogenous serum LH of less than 1.2 IU/L.

DOSAGE AND ADMINISTRATION

Treatment with PERGOVERIS should be initiated under the supervision of a physician experienced in the treatment of fertility problems. Self-administration of PERGOVERIS should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

In LH and FSH deficient women, the objective of PERGOVERIS therapy is to develop a single mature Graafian follicle from which the oocyte will be liberated following administration of human chorionic gonadotrophin (hCG). PERGOVERIS should be given as a course of daily injections. Since these patients are amenorrhoeic and have low endogenous oestrogen secretion, treatment can commence at any time. Nevertheless, the possibility of pregnancy should be first excluded by clinical or other means.

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

The majority of the women with very low LH levels (<1.2 IU/L as used in clinical studies, but this may vary from laboratory to laboratory) will have a poor ovarian response to r-hFSH alone. However, some women may have adequate follicular response. Clinicians will need to decide on a case by case basis whether to commence ovulation induction with r-hFSH alone or in combination with r-hLH.

The efficacy studies have suggested that the minimum effective daily dose of lutropin alfa is 37.5 IU. However, dose titration is recommended according to individual patient response.

Treatment should be tailored to the individual patient's response as assessed by measuring (i) follicle size by ultrasound and (ii) oestrogen response. A recommended regimen commences with one vial of PERGOVERIS daily. If less than one vial of PERGOVERIS daily is used, the follicular response may be unsatisfactory because the amount of 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 up to 5 weeks.

When an optimal response is obtained, a single injection of 250 microgram of recombinant hCG or 5,000 IU to 10,000 IU hCG should be administered 24-48 hours after the last PERGOVERIS injection. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination (IUI) may be performed. Luteal phase support should be considered since lack of endogenous gonadotrophins after ovulation may lead to premature failure of the corpus luteum.

If an excessive response is obtained, treatment with PERGOVERIS should be stopped and the trigger hCG injection withheld. Treatment should recommence in the next cycle at an FSH dosage lower than that of the previous cycle.

CONTRAINDICATIONS

PERGOVERIS is contraindicated in patients with:

- hypersensitivity to gonadotrophins or to any of the excipients
- ovarian, uterine or mammary carcinoma
- tumours of the hypothalamus or pituitary gland
- ovarian enlargement or cyst of unknown aetiology
- gynaecological haemorrhages of unknown origin
- pregnancy and lactation

PRECAUTIONS

Precautions

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. PERGOVERIS should not be used when an effective response cannot be obtained, such as ovarian failure, malformation of the sexual organs or fibroid tumours of the uterus that are incompatible with pregnancy. In addition, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and pituitary or hypothalamic tumours and appropriate specific treatment given.

Patients undergoing stimulation for follicular growth and induction of ovulation are at an increased risk of developing ovarian hyperstimulation syndrome (OHSS) in view of possible excessive oestrogen response and multiple follicular development.

Ovarian Hyperstimulation Syndrome (OHSS)

OHSS and multiple follicular development may occur as a possible excessive oestrogen response to stimulation of follicular growth and induction of ovulation. OHSS is a

syndrome that can manifest itself with various degrees of severity. In the WHO Technical Report Series No. 514 OHSS is classified into 3 grades:

- Grade 1: Variable ovarian enlargement, sometimes associated with small cysts. Laboratory findings include urinary oestrogen levels of over 150 microgram per 24 hours and pregnanediol excretion titres of over 10 mg/24 hours. Symptoms are minor;
- Grade 2: Patients in this category have additional symptoms like abdominal distension, nausea, vomiting and diarrhoea. Careful medical observation is required and appropriate symptomatic treatment is indicated;
- Grade 3: These patients are characterised by having large ovarian cysts, ascites, and sometimes hydrothorax. Haemoconcentration with increased blood, viscosity and coagulation abnormalities may appear.

OHSS is a medical event distinct from uncomplicated ovarian enlargement. It is characterised by an apparent dramatic increase in vascular permeability which can result in an accumulation of fluid in the peritoneal cavity, thorax, and rarely in the pericardial cavities. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting and weight gain. The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhoea, severe ovarian enlargement, weight gain, dyspnoea and oliguria. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax and rarely, acute pulmonary distress and thromboembolic events.

OHSS develops rapidly (within 24 hours to several days) and most often after treatment with follitropin or hCG has been discontinued, reaching its maximum at about seven to ten days following treatment. Patients, therefore, should be followed for at least two weeks after follitropin or hCG administration. Cases of OHSS are more common, more severe and more protracted if pregnancy occurs. Usually, OHSS resolves spontaneously with the onset of menses. Excessive oestrogenic response seldom gives rise to significant hyperstimulation unless hCG is administered to induce ovulation. It is therefore prudent to withhold hCG in such cases and advise the patient to refrain from intercourse for at least 4 days.

If OHSS occurs, treatment should be stopped and the patient hospitalised. Treatment is primarily symptomatic, consisting of bed rest, fluid and electrolyte management, and analgesics if needed. The phenomenon of haemoconcentration associated with fluid loss into the peritoneal cavity, pleural cavity and pericardial cavity has been seen to occur and should be thoroughly monitored in the following manner 1) fluid intake and output, 2) weight, 3) haematocrit, 4) serum and urinary electrolytes, 5) urine specific gravity 6) Blood Urea Nitrogen (BUN) and creatinine levels and 7) abdominal girth. These evaluations are to be performed daily or more often if the need arises. Appropriate imaging examination, especially ultrasound, should also be used for identifying, localising and quantifying fluid loss.

There is an increased risk of injury to the ovary with OHSS. The ascitic, pleural and pericardial fluids should not be removed unless absolutely necessary to relieve symptoms such as pulmonary distress or cardiac tamponade. Pelvic examination may cause rupture of an ovarian cyst, which may result in haemoperitoneum and should therefore be avoided.

If this does occur, and if bleeding becomes such that surgery is required, the surgical treatment should be designed to control bleeding and to retain as much ovarian tissue as possible.

Careful monitoring of ovarian response based on ultrasound is recommended prior to and during stimulation therapy, especially in patients with polycystic ovaries.

In patients undergoing induction of ovulation, the incidence of multiple pregnancies and births is increased compared with natural conception. The patient should be advised of the potential risk of multiple births before starting treatment.

To minimise the risk of OHSS or of multiple pregnancy, ultrasound scans as well as oestradiol measurements are recommended. In anovulation the risk of OHSS is increased by a serum oestradiol level >900 pg/mL (3,300 pmol/L) and more than 3 follicles of 14 mm or more in diameter.

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

Adherence to recommended PERGOVERIS dosage and regimen of administration and careful monitoring of therapy will minimise the incidence of OHSS and multiple pregnancy.

In clinical trials, lutropin alfa has been associated with higher oestradiol levels than follitropin alfa alone.

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, treatment with gonadotrophins may further increase the risk for aggravation or occurrence of such events. In these women, the benefits of gonadotrophin administration need to be weighed against the risks. It should be noted however, that pregnancy itself as well as OHSS also carry an increased risk of thromboembolic events.

In rare instances, thromboembolism has been associated with gonadotrophin therapy.

Hepatic/renal impairment

Caution should be used and close monitoring considered when administering PERGOVERIS to patients with renal or hepatic impairment. There are currently no data available on the use of PERGOVERIS in patients with hepatic or renal impairment.

Genotoxicity

Lutropin alfa was inactive in *in vitro* tests for gene mutation and chromosomal damage, and in an *in vivo* mouse micronucleus test. Follitropin alfa showed no genotoxic activity in a series of assays performed to evaluate its potential to cause gene mutations (*Salmonella typhimurium*, *E. coli* and Chinese hamster lung cells) and chromosomal damage (human lymphocytes and mouse micronucleus test).

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of follitropin alfa and lutropin alfa.

Congenital Malformations

The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This could be due to parental factors (eg, maternal age, genetics), ART procedures and multiple pregnancies.

Use in Pregnancy

Pregnancy Category D.

PERGOVERIS should not be administered during pregnancy as it may cause fetal harm when given to a pregnant woman (see CONTRAINDICATIONS). Treatment of pregnant rats and rabbits with r-hLH at subcutaneous doses of 10 IU/kg/day and above was associated with embryonic resorptions (approximately 0.4x and 0.8x clinical exposure at the maximum recommended clinical dose of 225 IU/day, based on body surface area, respectively). Teratogenicity was not observed in pregnant rats and rabbits dosed with r-hLH at subcutaneous doses up to 20 IU/kg/day (approximately 0.8x and 1.6x clinical exposure, based on body surface area, respectively). Administration of 10 IU/kg/day r-hLH to rats from late gestation to weaning resulted in adverse effects on the post-natal survival and growth of offspring.

In rats and rabbits, follitropin alfa caused dystocia and marked postimplantation loss at subcutaneous doses of greater than 5 IU/kg/day, indicating that it is embryotoxic and fetotoxic. Follitropin alfa was not teratogenic at subcutaneous doses up to 320 IU/kg/day in rats or 5 IU/kg/day in rabbits.

Ectopic pregnancy may also occur, especially in women with a history of prior tubal disease.

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

Use in Lactation

PERGOVERIS should not be administered during lactation (see CONTRAINDICATIONS). Secretion of r-hLH and/or its degradation products has been shown to occur in lactating rats. It is not known whether follitropin alfa is excreted in human milk. In lactating rats, follitropin alfa at doses up to 40 IU/kg did not influence lactation or have any effects on the postnatal growth and development of the offspring. Follitropin alfa was measured in the milk in early lactation.

ADVERSE EFFECTS

In clinical trials, a maximal score of all mild and moderate injection site reactions (bruising, pain, redness, itching or swelling) was reported in 12.7% (mild) and 2.7% (moderate) of the 2282 injections in 271 treatment cycles, respectively. Among the 170 patients treated, only 2 patients (1.2%) reported a severe injection site reaction.

OHSS was observed in 3.9% of treatment cycles with lutropin alfa. Six serious OHSS reports (2.3%) occurred in 259 treatment cycles.

In rare instances, thromboembolisms, adnexal torsion (a complication of ovarian enlargement), and haemoperitoneum have been associated with human menopausal gonadotrophin therapy. Although these adverse events were not observed, there is a possibility that they may also occur with PERGOVERIS. Intercourse should be prohibited in those patients in whom significant ovarian enlargement occurs after ovulation because of the danger of haemoperitoneum resulting from ruptured ovarian cysts.

The following common (>1/100 patients) undesirable effects are observed after administration of lutropin alfa and may occur during PERGOVERIS treatment:

Application site disorders:	injection site reaction
General disorders:	headache, somnolence
Gastro-intestinal system disorders:	nausea, abdominal pain,
Reproductive disorders:	ovarian hyperstimulation syndrome, ovarian cyst, breast pain, pelvic pain

The reported undesirable effects are consistent with those reported for other hLH-containing products.

In clinical trials, headaches have been reported. Local reactions at the injection site have been reported following gonadotrophin therapy and may occur during PERGOVERIS treatment.

The reactions reported below are classified according to frequency of occurrence as follows:

Very Common	$\geq 1/10$
Common	1/100 - 1/10
Uncommon	1/1000 - 1/100
Rare	1/10 000 - 1/ 1000
Very Rare	$\leq 1/10\ 000$

The following adverse effects have been reported during gonadotrophin therapy and may occur during PERGOVERIS treatment:

Body System as a whole

- Uncommon:* Hypersensitivity reactions (febrile reactions which may be accompanied by chills, musculoskeletal aches, joint pains, malaise, headache, fatigue, rash and hives). It is not clear whether these were pyrogenic responses or possible allergic reactions
- Very rare:* Mild systemic allergic reactions (e.g. mild forms of erythema, rash, facial swelling, urticaria, oedema, difficulty breathing). Serious cases of allergic reactions, including anaphylactic reactions and shock, have also been reported.

Dermatological

- Common:* Dry skin, hair loss

Application site

- Very common:* Mild to severe injection site reaction (pain, rash, bruising, swelling and/or irritation)

Reproductive

- Very common:* Ovarian cyst, mild to moderate ovarian enlargement
- Common:* Mild to moderate OHSS, breast tenderness, pelvic pain
- Uncommon:* Severe OHSS
- Rare:* Complications of severe OHSS (adnexal torsion associated with ovarian enlargement, haemoperitoneum, thromboembolism)

Gastrointestinal

- Common:* Abdominal pain, abdominal cramps, abdominal distension, abdominal discomfort, diarrhoea, nausea, vomiting

Central Nervous system

- Very common:* Headache
- Common:* Somnolence

Haematological

- Very Rare:* Thromboembolism usually associated with moderate to severe OHSS

Respiratory

- Very Rare:* Exacerbation or aggravation of asthma

Refer to PRECAUTIONS for information on symptoms and management of OHSS.

INTERACTIONS WITH OTHER MEDICINES

PERGOVERIS should not be administered as a mixture with other drugs in the same injection except follitropin alfa.

OVERDOSAGE

The effects of overdosage of PERGOVERIS are unknown, nevertheless there is a possibility that OHSS may occur which is further described in PRECAUTIONS.

Single doses of up to 40,000 IU of lutropin alfa have been administered to healthy female volunteers without serious adverse events and were well tolerated.

Please advise patients to immediately contact their doctor or the Poisons Information Centre (in Australia telephone 131 126, in New Zealand telephone 0800 764 766) if they are concerned that they have given themselves too much PERGOVERIS.

PHARMACEUTICAL PRECAUTIONS

Shelf-life:

36 months

PERGOVERIS must be reconstituted with the solvent before use and the reconstituted solution must be injected immediately as it contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Special Precaution for Storage:

The lyophilised product must be stored below 25°C. Protect from light.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

PERGOVERIS is supplied in packs of 1, 3 or 10 vials with the corresponding number of vials of solvent. Each vial of PERGOVERIS contains 150 IU (equivalent to 10.92 microgram) of follitropin alfa and 75 IU of lutropin alfa (equivalent to 3.0 microgram) as lyophilised powder.

FURTHER INFORMATION

Description

Human follicle stimulating hormone (FSH) is a glycoprotein (MW about 30,000 Da) and is characterised by two amino acid chains known as α and β . Follitropin alfa is a recombinant human follicle stimulating hormone (r-hFSH) produced by genetically

engineered Chinese Hamster Ovary (CHO) cells. Lutropin alfa is a recombinant human luteinising hormone (r-hLH). It is a glycoprotein (MW about 29,000 Da) that consists of two non-covalently linked, non-identical protein components designated as the α - and β -subunits. Recombinant-hLH is produced by genetically engineered Chinese Hamster Ovary cells.

The α chain is common to all gonadotropins (among them r-hFSH and r-hLH) with specificity residing in the β -chain. The β -chain confers biological activity.

The physicochemical, immunological and biological activities of r-hLH are comparable to those of human menopausal urinary-hLH (u-hLH).

The main difference between u-hLH and r-hLH is that the u-hLH carbohydrate moieties are essentially capped with sulphate groups, while in r-hLH it is with sialic acid. Preclinical and clinical experience, however, indicate that this has no significant impact on the pharmacokinetic characteristics of these molecules.

PERGOVERIS is available as a sterile, lyophilised powder in vials containing follitropin alfa 150 IU (equivalent to 10.92 microgram) and lutropin alfa 75 IU (equivalent to 3.0 microgram). It is intended for reconstitution with sterile Water for Injections. PERGOVERIS also contains polysorbate 20, sodium phosphate-dibasic dihydrate, sodium phosphate-monobasic monohydrate, sucrose, methionine, phosphoric acid and sodium hydroxide to adjust the pH as excipients. The pH of the reconstituted solution is 6.5-7.5.

Clinical Trials

The safety and efficacy of the combination of follitropin alfa and lutropin alfa have been examined in five studies for induction of ovulation in women with hypogonadotropic hypogonadism (HH).

Pivotal studies

The safety and efficacy of the combination of follitropin alfa and lutropin alfa administered concomitantly, subcutaneously, in females with hypogonadotropic hypogonadism for ovulation induction was assessed and confirmed in the following two international pivotal studies.

Study 6253

Study 6253 was a Phase II randomised, open-label, dose-finding study to determine the minimal effective dose and assess the safety of r-hLH to support r-hFSH-induced follicular development in LH and FSH deficient anovulatory women. Patients were randomised to treatment with 0, 25, 75 or 225 IU r-hLH concomitant with 150 IU of r-hFSH for up to 3 treatment cycles. Thirty-eight patients were enrolled and treated in a total of 53 treatment cycles.

The proportion of patients who fulfilled the primary efficacy endpoint criteria (at least one follicle ≥ 17 mm; $E_2 \geq 400$ pmol/L; mid-luteal phase $P_4 \geq 25$ nmol/L) was related to the dose of r-hLH, both when excessive follicular development was not included as a success (0.0%, 14.3%, 44.4% and 50.0% for treatment with 0, 25, 75 and 225 IU r-hLH, respectively; $p=0.0124$) and when excessive follicular development was included as a success (0.0%, 14.3%, 66.7% and 80.0% for treatment with 0, 25, 75 and 225 IU r-hLH, respectively; $p=0.0001$).

Study 21008

The safety and efficacy of lutropin alfa 75 IU administered subcutaneously in conjunction with follitropin alfa for induction of ovulation in women with hypogonadotropic hypogonadism and severe gonadotrophin deficiency was assessed in this Phase III double-blind, placebo-controlled, randomised trial of 39 women.

The primary efficacy parameter in this single-cycle study was follicular development as defined by: (i) at least one follicle with a mean diameter of ≥ 17 mm, (ii) pre-ovulatory serum E₂ level ≥ 109 pg/mL (400 pmol/L) and (iii) mid-luteal phase P₄ level ≥ 7.9 ng/mL (25 nmol/L). Patients with excessive follicular development or who became pregnant were considered treatment successes from the perspective of the analysis.

The efficacy results for Study 21008 are summarised in Table 1a.

Table 1a. Follicular Development Rate with *risk of OHSS* considered as a success, (Population: ITT Patients)

Follicular Development	Placebo and 150 IU r-hFSH (n=13) n (%)	75 IU r-hLH and 150 IU r-hFSH (n=26) n (%)	Total (n=39) n (%)	p-value ^(a)
Yes	2 (15.4)	17 (65.4)	19 (48.7)	0.006
No	11 (84.6)	9 (34.6)	20(51.3)	

(a) Fisher's Exact Test

However the efficacy results for the same study are also assessed when risk of OHSS is considered as an efficacy failure in Table 1b.

Table 1b. Follicular Development Rate and Ovulation with *risk of OHSS* considered as an efficacy failure, (Population: ITT Patients)

Follicular Development	Placebo and 150 IU r-hFSH (n=13) n (%)	75 IU r-hLH and 150 IU r-hFSH (n=26) n (%)	Total (n=39) n (%)	p-value ^(a)
Yes	1 (7.7)	11 (42.3)	12 (20.8)	0.034
No	12 (92.3)	15 (57.7)	27 (69.2)	

Other Studies

The safety and efficacy of lutropin alfa administered subcutaneously concomitantly with follitropin alfa for ovulation induction in females with hypogonadotropic hypogonadism was also investigated in three additional studies.

Study 6905 was a Phase II/III open-label, randomised, multicentre study to determine the minimal effective dose and assess the safety of lutropin alfa administered with follitropin alfa to induce follicular development in anovulatory women with hypogonadotropic hypogonadism and moderate gonadotrophin deficiency. Forty patients were enrolled and treated.

Study 7798 was a Phase III multicentre study to assess the efficacy and safety of lutropin alfa administered with follitropin alfa for up to three treatment cycles in induction of

follicular development in LH and FSH deficient anovulatory women and enrolled 15 patients.

Study 8297 was a Phase III multicentre, non-comparative study to assess the efficacy and safety of lutropin alfa administered with follitropin alfa for up to three treatment cycles in induction of follicular development in LH and FSH-deficient anovulatory women and enrolled 38 patients.

Among the 170 hypogonadotropic hypogonadal patients enrolled in the 5 lutropin alfa development studies, 154 were seeking fertility and of these 127 were treated with lutropin alfa. Overall 41 of 127 (32%) lutropin alfa treated patients (all doses) and 31 of 100 (31%) in the lutropin alfa 75 IU dose group achieved a pregnancy over a total of 205 treatment cycles (see Table 2 below).

Table 2 Summary of pregnancies in cycles of women wishing to conceive

Treatment	Placebo or no r-hLH				All r-hLH treated cycles					
	GF 6253	21008	GF 6905	Total no LH	GF 6253	21008	GF 6905	GF 7798	GF 8297	Total LH
Cycles	8	13	19	40	31	26	33	33	85	208
Cycles with hCG	2	3	15	20	17	13	30	28	64	152
Clinical pregnancies	0	1	4	5	3	1	8	7	15	34
Miscariages	0	0	1	1	1	0	1	2	1	5
Pregnancy loss after 20 weeks	0	0	0	0	0	0	0	1	1	1
Live birth single	0	0	2	2	1	0	3	3	9	16
Live birth multiple	0	1 (twins with 1 NND*)	1	2	1	0	3	2	4	10
Lost to follow up	0	0	0	0	0	1	1	0	0	2

* NND neonatal dead

NAME AND ADDRESS OF THE SPONSOR

Supplied in New Zealand by:

Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks, Auckland

Supplied in Australia by:

Merck Serono Australia Pty Ltd
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Frenchs Forest NSW 2086

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