NEW ZEALAND DATA SHEET

1 PRODUCT NAME

PERGOVERIS® 150 IU/75 IU powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PERGOVERIS contains follitropin alfa (recombinant human follicle stimulating hormone (r-hFSH)) and lutropin alfa (recombinant human luteinising hormone (r-hLH)) produced by genetically engineered Chinese Hamster Ovary (CHO) cells. 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.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for injection in vial(s).

PERGOVERIS is presented as a sterile, white to off-white lyophilised powder. It is intended for reconstitution with sterile water for injections. The pH of the reconstituted solution is 6.5-7.5.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with PERGOVERIS should be initiated under the supervision of a physician experienced in the treatment of fertility problems. The injection site should be alternated daily to prevent lipoatrophy. 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.

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 once 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.

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.

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.

PERGOVERIS is for single use in one patient only. Discard any residue.

4.3 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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. It is recommended that PERGOVERIS is not used in conditions where an effective response is usually not expected, such as primary 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 and hyperprolactinemia, and appropriate specific treatment given.

Ovarian Hyperstimulation Syndrome (OHSS)

A certain degree of ovarian enlargement is an expected effect of controlled ovarian stimulation. It is more commonly seen in women with polycystic ovarian syndrome and usually regresses without treatment.

Distinct from uncomplicated ovarian enlargement, OHSS is a condition that can manifest itself with various degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal cavity, pleural, and rarely, in the pericardial cavities.

Mild to moderate OHSS is a common adverse effect of ovulation induction with gonadotrophins; the risk should be considered and discussed with women prior to treatment.

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, dyspnoea and oliguria. Clinical evaluation may reveal signs such as hypovolaemia, haemoconcentration, 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, ischaemic stroke or myocardial infarction.

Independent risk factors for developing OHSS include young age, lean body mass, polycystic ovarian syndrome (PCOS), higher doses of exogenous gonadotrophins, high absolute or rapidly rising serum oestradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in Assisted Reproductive Technology (ART) cycles. In clinical trials, lutropin alfa has been associated with higher oestradiol levels than follitropin alfa alone.

Adherence to recommended PERGOVERIS and FSH dosage and regimen of administration and careful monitoring of therapy will minimise the incidence of OHSS. Monitoring of stimulation cycles by ultrasound scans, as well as oestradiol measurements, is recommended to identify risk factors early.

OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event. It most often occurs after treatment with follitropin or hCG has been discontinued, reaching its maximum at about seven to ten days following treatment. Therefore, patients should be followed for at least two weeks after follitropin or hCG administration.

There is evidence to suggest that hCG plays a key role in triggering OHSS and that the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, if monitoring results indicate a high risk of OHSS or if signs of ovarian hyperstimulation occur, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or use barrier contraceptive methods for at least 4 days. 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.

Mild or moderate OHSS usually resolves spontaneously with the onset of menses. If severe OHSS occurs, it is recommended that treatment be stopped, the patient be hospitalised and appropriate therapy started. 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 determinations 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.

Multiple pregnancy

In patients undergoing induction of ovulation, the incidence of multiple pregnancy is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancies, especially higher order, carry an increased risk of adverse maternal and perinatal outcomes. The patient should be advised of the potential risk of multiple births before starting treatment.

To minimise the risk of twins or higher order multiple pregnancy, careful monitoring of ovarian response is recommended. Appropriate management, such as cycle cancellation, should be considered in line with current clinical practice.

In patients undergoing ART procedures, the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient's age. Single embryo transfer in good prognosis cycles substantially reduces the risk of multiple pregnancy with little effect on live birth rates.

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.

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

Porphyria

In patients with porphyria or a family history of porphyria, PERGOVERIS may increase the risk of an acute attack. Deterioration or a first appearance of this condition may require cessation of treatment.

Congenital anomalies

The prevalence of congenital anomalies after the use of ART may be slightly higher than after spontaneous conceptions. Possible contributing factors include aspects inherent in the couple's infertility, ovulation induction agents, other medicines used in treatment and the ART procedures. While there is no specific evidence from clinical trials or post-marketing data implicating gonadotrophin use in adverse effects on pregnancy, embryonal or fetal development, parturition or postnatal development, ovulation induction agents cannot be excluded as a contributing factor.

Use in hepatic or 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.

Use in the elderly

No data available

Paediatric use

No data available

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See Section 4.1 THERAPEUTIC INDICATIONS.

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 Section 4.3 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 post implantation 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.

Use in lactation.

PERGOVERIS should not be administered during lactation (see Section 4.3 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive or use machines have been performed. However, adverse events of this medicine include dizziness which could affect the ability to drive or use machines (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

PERGOVERIS is a fixed dose combination product, containing lutropin alfa and follitropin alfa. In this context, undesirable effects may be due to either or both of these substances, or to their pharmacodynamic consequences.

In clinical trials with lutropin alfa, 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 very rare instances, thromboembolisms 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. Ovarian cysts and enlargements are common. Complications including adnexal torsion and haemoperitoneum have been reported rarely with human menopausal gonadotrophin therapy.

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

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

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

Very Common	≥ 1/10
Common	1/100 - 1/10
Uncommon	1/1000 - 1/100
Rare	1/10 000 - 1/1000
Very Rare	≤ 1/10 000

General disorders and administration site conditions

Very common: injection site reaction (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

Reproductive system and breast disorders

Very common: ovarian cyst, mild to moderate ovarian enlargement

Common: mild or moderate OHSS (including symptomatology), breast pain, pelvic pain

Uncommon: severe OHSS (including symptomatology)

Rare: complications of severe OHSS, ectopic pregnancy, adnexal torsion associated with ovarian enlargement

Gastrointestinal disorders

Common: abdominal pain, abdominal distension, abdominal discomfort, diarrhoea, nausea, vomiting

Nervous system disorders

Very common: headache, dizziness

Vascular disorders

Very rare: thromboembolism, usually associated with severe OHSS

Respiratory, thoracic and mediastinal disorders

Very rare: exacerbation or aggravation of asthma

Immune system disorders

Very rare: mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for information on symptoms and management of OHSS.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems in Australia, or at https://nzphvc.otago.ac.nz/reporting/ in New Zealand.

4.9 OVERDOSE

The effects of overdosage of PERGOVERIS are unknown, nevertheless there is a possibility that OHSS may occur which is further described in Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 and has a large extracellular domain. The *in vitro* binding affinities of r-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 ovulation and corpus luteum formation. 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 r-hLH is an increase in oestradiol secretion by the follicles, while administration of r-hFSH primarily stimulates the growth and maturation of the follicles.

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 as the optimal well-established, surrogate marker of conception was consistently found in 66.7% of patients with LH < 1.2 IU treated with 150 IU follitropin alfa and 75 IU lutropin alfa. This result was based on studies 6253 [66.7%] and 21008 [66.7%] and was calculated when risk of ovarian hyperstimulation syndrome (OHSS) and pregnancy outcome were considered as treatment successes. When patients with risk of OHSS were considered as a treatment failure, adequate follicular development was found in 43.2% of patients (combined analysis of follicular development in studies 6253 and 21008).

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 women with HH 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 HH 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 E_2 level ≥ 109 pg/mL (400 pmol/L) and (iii) mid-luteal phase P_4 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

The efficacy results for the same study are also assessed when the 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)	

(a) Fisher's Exact Test

Other Studies

The safety and efficacy of lutropin alfa administered subcutaneously concomitantly with follitropin alfa for ovulation induction in women with HH 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 patients with HH 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					
Study	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[1]	**0**	**1**	**4**	**5**	**3**	**1**	**8**	**7**	**15**	**34**
Miscarriages	**0**	**0**	**1**	**1**	**1**	**0**	**1**	**2**	**1**	**5**
Pregnancy loss after 20 weeks	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**
Live birth single	**0**	**0**	**2**	**2**	**1**	**0**	**3**	**3**	**9**	**16**
Live birth multiple	**0**	**1 (twins with 1 NND[2])**	**1**	**2**	**1**	**0**	**3**	**2**	**4**	**10**
Lost to follow up	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**0**	**2**

[1] Clinical pregnancy was defined by an ultrasound detection of a sac with or without heartbeat activity on day 35-42 after hCG administration
[2] NND neonatal death

5.2 PHARMACOKINETIC PROPERTIES

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.

5.3 PRECLINICAL SAFETY DATA

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Polysorbate 20, dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, sucrose, methionine, phosphoric acid and sodium hydroxide.

6.2 INCOMPATIBILITIES

Refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

3 years

Information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG) in Australia or on Medsafe Product Detail in New Zealand. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

PERGOVERIS must be reconstituted with the solvent before use and the reconstituted solution must be injected immediately as it contains no antimicrobial agent.

6.5 NATURE AND CONTENTS OF CONTAINER

PERGOVERIS is supplied in packs of 1, 3 or 10 glass vials with the corresponding number of glass vials of solvent.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

PERGOVERIS contains recombinant human follicle stimulating hormone (follitropin alfa (rch)) and recombinant human luteinising hormone (lutropin alfa (rch)).

Human follicle stimulating hormone (hFSH) is a glycoprotein (Molecular Weight (MW) about 30,000 Da) and is characterised by two amino acid chains known as α and β.

Recombinant human follicle stimulating hormone (r-hFSH) is a human gonadotrophin 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 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.

Human luteinising hormone (hLH) 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 human luteinising hormone (r-hLH) is a human gonadotrophin 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.

For both r-hFSH and r-hLH, the α-chain is common to all gonadotrophins family, 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.

CAS number

CAS-146479-72-3 (follitropin alfa); CAS-152923-57-4 (lutropin alfa); CAS-56832-30-5 (α-subunit, lutropin alfa); CAS-53664-53-2 (β-subunit, lutropin alfa).

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

Supplied in Australia by:

Merck Healthcare Pty Ltd

Suite 1, Level 1, Building B

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9 DATE OF FIRST APPROVAL

30 September 2010

10 DATE OF REVISION

9 March 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Updated the details of the Australian sponsor