Australian Government

Department of Health and Ageing

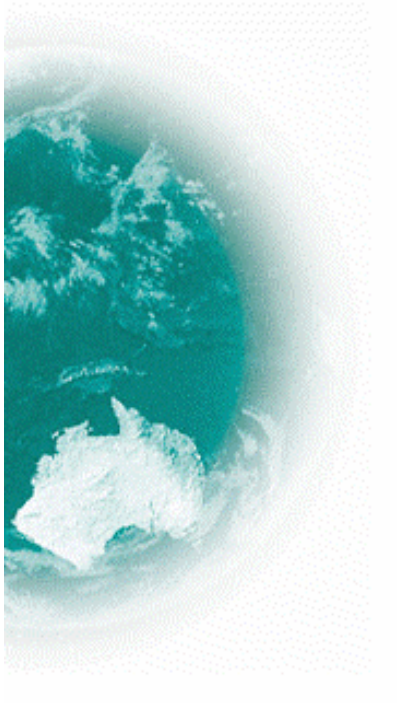
Therapeutic Goods Administration

Australian Public Assessment Report
for
Follitropin alfa (rch) and Lutropin alfa (rch)

Proprietary Product Name: Pergoveris

Submission No: PM-2008-1439-5

Sponsor: Merck Serono Australia Pty Ltd



January 2010

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	New Fixed Combination
Decision:	Approved
Date of Decision	10 November 2009
Active ingredient(s):	Follitropin alfa rch and Lutropin alfa rch
Product Name(s):	Pergoveris
Sponsor's Name and Address	Merck Serono Australia Pty Ltd Units 3 & 4 25 Frenchs Forest Road East Frenchs Forest NSW 2086
Dose form(s):	Powder for injection
Strength(s):	rhFSH – 150 IU; rhLH – 75 IU
Container(s):	Vial with a vial of diluent (sterile WFI)
Pack size(s):	Packs of 1, 3 or 10 vials with the same number of vials of diluent.
Approved Therapeutic use:	Stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials, these patients were defined by an endogenous serum LH < 1.2IU/L.
Route(s) of administration:	Subcutaneous injection
Dosage:	A recommended regimen commences with one vial of Pergoveris daily. Treatment should be tailored to the individual patient's response as assessed by measuring (i) follicle size by ultrasound and (ii) oestrogen 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.

Product Background

Combined severe FSH and LH deficiency is a rare disorder of reproductive function of both men and women. The disorder is characterised by the absence of effective hypothalamic-pituitary secretory activity, resulting in arrested or attenuated gonadal function. In women, the disorder may therefore present as failure to undergo the usual physical and reproductive changes of puberty or, if occurring after puberty, may present as amenorrhoea. Amenorrhoea is a manifestation of low oestrogen production, and is associated with adverse effects similar to those occurring in postmenopausal women: bone mineral abnormalities, altered lipid profiles, and accelerated cardiovascular disease. The additional consequence of arrested ovarian function is infertility. From the clinical perspective, the diagnosis of severe FSH and LH deficiency is confirmed by endocrine testing, which demonstrates low oestrogen levels in association with low serum gonadotropin levels.

Merck Serono Australia Pty Ltd has applied to register Pergoveris, a new fixed-dose combination of follitropin alfa (rch) [recombinant human follicle stimulating hormone (FSH)] and lutropin alfa (rch) [recombinant human luteinising hormone (LH)], to be used for the stimulation of follicular

development in women with severe LH and FSH deficiency. The recommended dosing regimen is daily SC injection of 150 IU follitropin alfa and 75 IU lutropin alfa (i.e., one vial) until development of a single mature Graafian follicle.

The single agent products, lutropin alfa (rch) [Luveris] and follitropin alfa (rch) [Gonal-F], are approved for use for this indication in free combination at the dose levels proposed for Pergoveris.

Regulatory Status at the Time of Submission

This new fixed dose combination is of two currently registered products, Luveris (lutropin alfa (rch)) (ARTG numbers 90345, 95042) and GONAL-f (follitropin alfa (rch)) (ARTG numbers 81623, 91562, 91563, 91564, 93043, 93044, 93506, 96114, 96230, 96236, 96237).

A similar application has been submitted and approved in the EU (25 June 2007), Switzerland (13 May 2008) and Argentina (29 December 2008). Applications have been submitted in Canada, Bangladesh, Chile, Colombia, Indonesia, South Korea, Peru and Ukraine which are under evaluation. No applications have been submitted to the USA or New Zealand.

Product Information

The approved product information current at the time this AusPAR was developed is contained at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The drug substances, follitropin alfa and lutropin alfa are human glycoprotein hormones which consist of two non-covalently linked α and β-subunits. The common α-subunit is composed of 92 amino acids carrying two carbohydrate moieties linked to Asn-52 and Asn-78 and is identical for both gonadotropins. The follitropin β-subunit is composed of 111 amino acids carrying two carbohydrate moieties linked to Asn-7 and Asn-24. The lutropin β-subunit is composed of 121 amino acids carrying one carbohydrate moiety linked to Asn-30. Both gonadotropins are derived from genetically engineered Chinese Hamster Ovary cell lines.

The two active ingredients in the drug substance are manufactured by the processes approved for Gonal-F (follitropin alfa (rch)) in the original 1995 submission and as modified for a serum-free process in 2006 and Luveris (lutropin alfa (rch)) in its 1999 submission.

Thus, the manufacture of the two drug substances has already been approved (rhFSH for Gonal-F and rhLH for Luveris). Manufacture of the drug substances was therefore not evaluated.

The proposed specifications for the drug substances are the same as those used to release the drug substances for Gonal-F and Luveris.

Drug Product

The product is presented as a lyophilised powder in a vial. The single strength fixed dose is 10.92µg (~150IU) of follitropin alfa (rch) and 3.0µg (~75IU) lutropin alfa (rch).

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.

The pack sizes of the product are 1, 3 and 10 vials with the same number of vials of diluent (sterile WFI) in a cardboard carton. A syringe is required for reconstitution and injection but is not supplied with the pack.

1mL of the diluent is taken up into the syringe and injected into the vial of powder. The powder is dissolved and the solution taken up into the syringe and injected subcutaneously into the lower abdominal area or thigh.

The product is manufactured by preparing the excipients solution; thawing the drug substance and mixing the compounded solution. This is sterilised by filtration and the sterile solution is filled into type I glass vials, freeze-dried, stoppered and sealed.

The proposed specifications, which control identity, potency, purity and other physical, chemical and microbiological properties relevant to the clinical use of the product are satisfactory. Appropriate validation data have been submitted in support of the test procedures.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data were not presented as Gonal-f and Luveris are not photostable. The product should therefore be protected from light.

The proposed shelf life is 3 years when stored below 25°C.

As the instructions for use are to reconstitute and inject immediately, no in-use stability data were submitted.

The labelling and PI include the warning "Product is for single use in one patient only. Discard any residue."

Biopharmaceutics

In support of this submission, the company submitted two bioavailability studies:

1. Study IMP23718: to assess the relative bioavailability of FSH and the tolerability of the test product compared to Gonal-F (follitropin alfa).

2. Study IMP23722: to assess the relative bioavailability of LH and the tolerability of the test product compared to Luveris (lutropin alfa).

Study IMP23718

This study was a two-arm. cross-over, double-blind Phase I study to assess the relative bioavailability of FSH and the tolerability of the fixed combination of r-hFSH/r-hLH and Gonal-F, following single subcutaneous injections in down-regulated healthy female volunteers (FSH = follitropin, LH = lutropin).

The pharmacokinetic results were accepted as valid.

Statistical Analysis

Analyte: FSH (n = 35)

Single dose, prompt release	T_{max} (h)	C_{max}	AUC_{0-t}
Treatment			
A: (Reference product)	16.2±7.10 (6.0-24.0)	10.3±2.22 (5.40-16.2)	918±182 (571-1350)
B: (Test product)	16.4±7.51 (9.0-36.0)	10.3±1.99 (5.80-13.6)	925±175 (677-1530)
Statistical analysis:	***median diff. (h)***	***ratio***	***ratio***

A vs. B Estimate	No significant difference	1.00	1.00
90% CI*	-	0.96-1.04	0.99-1.04

* - corrected for baseline (n = 34)

The $AUC_{0-\infty}$ was not calculated due the presence of endogenous concentrations (baseline, due to insufficient down regulation of endogenous FSH) and many profiles approached a flat line towards the end as the serum levels were returning to baseline. The statistical analysis was corrected for baseline.

Assessment

The 90% CI for AUC_{0-t} and C_{max} for the test product versus Gonal-F were within the range 0.80-1.25 for FSH, as required to conclude bioequivalence.

Study IMP23722

This study was a two arm-cross-over, open-label Phase I study to assess the relative bioavailability of LH and the tolerability of the fixed combination of r-hFSH/r-hLH and Luveris, following single subcutaneous injections in down-regulated healthy female volunteers.

The pharmacokinetic results were accepted as valid.

Statistical Analysis

Analyte: LH (n = 71 for reference and n = 73 for test)

Single dose, prompt release	**T_{max} (h)**	**C_{max}**	**AUC_{0-t}**
Treatment			
A: (Reference product)	7.59±1.82 (4.0-12.0)	9.74±3.46 (3.60-22.0)	235±137 (58.7-674)
B: (Test product)	7.58±2.19 (3.95-15.0)	9.00±3.34 (4.20-26.0)	208±118 (60.3-616)
Statistical analysis#:	***median diff. (h)***	***ratio***	***ratio***
A vs. B Estimate	No significant difference	0.97	0.98
90% CI*	-	0.92-1.02	0.90-1.06

* - baseline included as a covariate

- performed on 63 subjects

Analyte: FSH (n = 73)

Single dose, prompt release	**T_{max} (h)**	**C_{max}**	**AUC_{0-t}**
Treatment			
A: (Test product)	16.5±8.23 (8.95-48.0)	25.6±5.38 (15.8-42.0)	1990±338 (1480-3240)

The $AUC_{0-\infty}$ was not calculated due the presence of endogenous concentrations (baseline, due to insufficient down regulation of endogenous FSH) and many profiles approached a flat line towards the end as the serum levels were returning to baseline. This was acceptable.

It was stated that the statistical analysis showed a period effect for C_{max} and $AUC_{0-\infty}$ when baseline adjustment was not included.

Assessment

The 90% CI for AUC_{0-t} and C_{max} for the test product versus Luveris were within the range 0.80-1.25 for LH, as required to conclude bioequivalence.

Conclusion

The test product "Pergoveris" containing follitropin alfa and lutropin alfa is bioequivalent to the two reference products Gonal-F and Luveris containing the single entity follitropin alfa and lutropin alfa, respectively.

Quality Summary and Conclusions

The administrative, product usage, biological, pharmaceutical and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. There are no issues of concern. With regard to quality issues, the evaluator recommended approval of the product.

III. Non-Clinical Findings

Introduction

The non-clinical overview and summaries contained extensive references to previously evaluated studies submitted to support the registration of the single agent follitropin alfa (rch) (Gonal-F) and lutropin alfa (rch) products (Luveris). A single new study examining local tolerance of the clinical formulation in rabbits, and a small number of published papers, were submitted in support of this application.

Pharmacology

Recombinant human FSH and recombinant human LH were shown to exert an additive effect on oocyte maturation *in vitro* (rat follicles) in a newly submitted published paper (Törnell *et al*., 1995) and on the promotion of follicle growth and oestradiol production *in vivo* (monkeys; IM administration) in a previously submitted study.

Pharmacokinetics

No new non-clinical pharmacokinetic data were submitted. The Clinical Overview indicated that the pharmacokinetic profiles of follitropin alfa and lutropin alfa were unchanged with the proposed fixed-dose combination product compared with the single agent products.

Toxicology

The newly submitted local tolerance study was the only toxicity study submitted involving dosing with follitropin alfa and lutropin alfa together. The study was adequately conducted and performed according to GLP. It revealed no treatment-related injection site reactions or other adverse effects in rabbits following subcutaneous (SC) administration of the clinical formulation (single or 7-day repeat daily dosing; 1 mL) or a formulation 3-times higher in strength (single 2 mL dose).

Non-Clinical Summary and Conclusions

Recombinant human FSH and LH have an additive effect on oocyte maturation (shown *in vitro* in the rat and *in vivo* in the monkey). Since no differences were observed in the human PK profile of the two active substances when administered in combination compared with separate administration, there were no new animal pharmacokinetic data submitted. A single new non-clinical study, examining local tolerance of the proposed combination product, was submitted. It showed no adverse effects following SC administration of the clinical formulation at the proposed strength (single or repeat daily dosing for 7 days) or at 3-times the clinical strength (single dose) in rabbits.

There were no non-clinical objections to the registration of Pergoveris for the proposed indication.

IV. Clinical Findings

Introduction

The sponsor initially requested the following indication:

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

Clinical data submitted with the application comprised two comparative bioequivalence studies, each separately comparing the combination product with one of its constituents. This procedure was adopted because known pharmacokinetic data suggested that for an accurate assessment of bioequivalence, (a) different dosages of the combination product would be required in assessing the two constituents, and (b) appropriate sample sizes required to assess relative bioavailability would differ. Thus, the first (Study IMP 23718) compared the dose follitropin alfa (rch) 300 IU + lutropin alfa (rch) 150 IU (as Pergoveris) to follitropin alfa (rch) 300 IU (as Gonal-F), and the second (Study IMP 23722) compared the dose follitropin alfa (rch) 900 IU + lutropin alfa (rch) 450 IU (as Pergoveris) to lutropin alfa (rch) 450 IU (as Luveris).

Study IMP 23718 was double-blind, and study IMP 23722 was open-label. No explanation was offered for this difference, but it was not considered important in the circumstances. Individual subject data were provided. The test product used in the studies (Pergoveris) was declared to be identical to that proposed for registration.

No new efficacy or safety studies with Pergoveris (fixed dose combination of follitropin alfa (rch) and lutropin alfa (rch)) were submitted in this application since proof of efficacy and safety relied upon data previously approved by the TGA for registration of Luveris (lutropin alfa (rch)). Efficacy data from the Luveris submission were not re-evaluated for the registration of Pergoveris. However, the clinical evaluator did review the previous clinical evaluation report for Luveris.

Clinical efficacy and safety of lutropin alfa administered in free combination with follitropin alfa in patients with primary or secondary anovulation were demonstrated in two phase II/III studies: 6253 and 6905, which were both prospective, randomised, open, parallel group dose finding studies investigating three doses of lutropin alfa together with a fixed dose of 150 IU follitropin alfa and a control group with 150 IU follitropin alfa only.

Pharmacokinetics

Study IMP23718

This was a study comparing the bioequivalence of (a) FSH in the fixed combination product which is the subject of the present application to (b) FSH administered as the product Gonal-F. Sample size was based on assumed intrasubject variability of approximately 20% and true mean ratio for AUC (test/reference) lying between 0.90 and 1.10. For these hypothesised values, a sample size of 29 evaluable subjects was required for demonstrating bioequivalence with 70% power, using the

acceptance range of 0.8 to 1.25. Thirty-six subjects were recruited in order to have at least 30 evaluable subjects.

Admission criteria included:

- Premenopausal woman aged 18-40.
- Took combined oral contraceptive pill for ≥ 2 cycles prior to enrolment.
- Normal FSH and LH baseline. Women with serum FSH > 13 IU/L were ineligible; women with serum FSH ≤ 13 were accepted for down-regulation.
- Weight ≥ 50 kg; BMI ≤ 28.
- Smoked < 10 cigarettes/day, and agreed to smoke < 5 cigarettes/day for the duration of the study.

Exclusion criteria included:

- Any clinically significant abnormality in pre-study laboratory tests.
- Used any prescription drugs within 12 weeks before study entry.

Additional medication could be taken without exclusion from the study at the discretion of the investigator.

Following blood testing for serum FSH and LH, subjects attended for Zoladex treatment on Day DR1. They continued taking their OC until Day DR7, then recommenced at the end of the study (Day SD1). There was provision for withdrawal of a subject from the study if down-regulation was not confirmed. Subjects were instructed not to consume foods containing grapefruit juice, alcohol, or xanthines from 48 hours before investigational drug administration until discharge from the study facility. They were admitted to the facility on the evening before each planned administration of investigational drug, and remained there until 24 hours after injection. Subjects fasted from at least 8 hours before each treatment until 4 hours after. Water was freely available at all times. Blood was sampled pre-dose, then immediately after injection (approximately 9 am), then at 1, 2, 4, 6, 9, 12, 15, 24, 36, 48, 60, 72, 96, 120, 144 and 168 hours after dosing.

All subjects were successfully down-regulated (as demonstrated by serum FSH ≤ 4 IU/L) before the first study drug administration. Two subjects (one from each treatment order) were withdrawn from the study before the second injection, due to high FSH levels. All other subjects completed the study.

Results

Values of C_{max}, AUC_{0-t} (AUC from time zero to last measurable time point as calculated by linear trapezoidal method) and T_{max} were calculated. Table 1 shows results based on all the data (including data from the 2 subjects who did not complete the study). AUC_{∞} was not calculated as endogenous concentrations (baseline) were present for all subjects due to insufficient down-regulation of endogenous FSH. Baseline values of FSH were observed for both periods in all subjects, with higher levels in all but one subject in period 2 compared to period 1. The median pre-dose value was 1.46 IU/L for period 1 and 2.60 IU/L for period 2.

Table 1: Pharmacokinetic Studies

Design	Treatments	Subjects entered	Pharmacokinetics r-hFSH			Adverse reactions
			C_{max} Geo. Mean (%CV) IU/L	AUC_{0-t} Geo. Mean (%CV) h. IU/L	T_{max} Median (range) h	
IMP23718 Double-blind, randomised, single dose, two-period crossover bioequivalence study.	Initial pituitary downregulation using Zoladex 3.6 mg SC. Test product r-hFSH 300 IU + r-hLH 150 IU as Pergoveris. Comparator r-hFSH 300 IU as Gonal-F. Washout period 7 days between treatments.	36 healthy premenopausal women randomised and received Zoladex: Mean age 24.2 (sd 4.3); mean weight 63.4 kg (sd 6.1). 34 completed	10.1 (21.0) N=35 10.1 (22.7) N=35	911 (18.1) N=35 901 (19.7) N=35	12.1 (9-36) N=35 12.0 (6-24) N=35	No serious AEs; no withdrawals due to AE. 61 AEs recorded during study: 21/61 after Zoladex; 20/61 after Pergoveris; 20/61 after Gonal-F. 7, 8, and 9 subjects reported headache after Zoladex, Pergoveris and Gonal-F respectively. No other AE was reported by >2 subjects after any one of these treatments.

Perusal of individual subject pharmacokinetic measurements showed that one subject showed a 5- to 10-fold higher peak than all other individuals following administration of the fixed combination, with a typical profile for LH. No explanation could be found for this unexpected occurrence; neither in the clinical unit nor in the laboratory at sample analysis was anything unusual noted. A repeated analysis of the back-up samples for that subject confirmed the measured serum concentrations. This subject was excluded from the bioequivalence analysis. Curves for the other subjects did not raise any concerns.

Pharmacokinetic parameters were analysed using an ANOVA model which included sequence, subjects nested within sequence, period and treatment as factors. The calculated ratios and 90%

confidence intervals for the antilogs of geometric least squares means of log-transformed parameters are tabulated below. Bioequivalence was demonstrated using the pre-specified acceptance interval (0.80, 1.25).

Parameter	Ratio Test/Reference (90% CI)
C_{max}	1.00 (0.96, 1.04)
AUC_{0-t}	1.01 (0.99, 1.04)

The trial protocol included the provision: "Although not expected as subjects are down-regulated, baseline values will be appropriately integrated into the calculation." Accordingly, in view of the baseline FSH measurements described above, the data were also analysed using a model which included baseline FSH as a covariate. The effect on the bioequivalence calculation was insignificant.

Study IMP23722

This was a study comparing the bioequivalence of (a) LH in the fixed combination product which is the subject of the present application to (b) LH administered as the product Luveris. Sample size was originally based on assumed intrasubject variability of approximately 30% and true mean ratio for AUC (test/reference) lying between 0.95 and 1.05. For these hypothesised values, a sample size of 39 evaluable subjects was required for demonstrating bioequivalence with 80% power, using the acceptance range of 0.8 to 1.25. It was planned to recruit 46. Because of inadequate recruitment at the original study centre, another centre was added, and in view of the possibility of increased heterogeneity, the estimated value for intrasubject variation was raised to 38%. The required sample size increased to 55-60. 81 healthy premenopausal female subjects entered the treatment phase over the two investigational sites and were included in the safety analysis. 18 subjects were withdrawn from the study prior to Period 2, mainly due to failure of down-regulation. A total of 63 subjects successfully completed the study and were included in the evaluation of bioequivalence.

Inclusion and exclusion criteria were as for Study IMP23718.

Blood was sampled pre-dose, and dosing was at about 8 am. Blood was then drawn for serum LH measurement at 1, 2, 4, 6, 9, 12, 15, 24, 36, 48, 60, 72, 96 and 120 hours after dosing.

Results

Results are shown in Table 2 based on all the data (including data from the 18 subjects who withdrew after completing period 1).

Table 2: Pharmacokinetic Studies

IMP23722 Open-label, randomised, single dose, two-period crossover bioequivalence study.	Initial pituitary downregulation using Zoladex 3.6 mg SC. Test product r-hFSH 900 IU + r-hLH 450 IU as Pergoveris. Comparator r-hLH 450 IU as Luveris. Washout period ≥21 days between treatments.	81 healthy premenopausal women randomised and received Zoladex: Mean age 27.4 (sd 5.6); mean weight 63.42 kg (sd 7.2). 63 completed	8.5 (35) N=73 9.1 (37) N=71	182 (55) N=73 199 (65) N=71	6.1 (4-15) N=73 8.9 (4-12) N=71	No serious AEs. 1 withdrawal due to AE: severe AE ("emotionally labile"), following administration of the test product.

AUC_{∞} was not calculated as endogenous concentrations (baseline) were present for several subjects (see above). Individual subject measurements were unremarkable. Pharmacokinetic parameters were analysed using an ANOVA model as described above, omitting the data from non-completers. Baseline LH values were included as a covariate. The calculated ratios and 90% confidence intervals for the antilogs of geometric least squares means of log-transformed parameters are tabulated below, based on the data for the 63 completers. Bioequivalence was demonstrated using the pre-specified acceptance interval (0.80, 1.25).

Parameter	**Ratio Test/Reference (90% CI)**
C_{max}	0.97 (0.92, 1.02)
AUC_{0-t}	0.98 (0.90, 1.06)

The evaluator stated that the studies appeared to have been carefully conducted and analysed.

The baseline gonadotrophin findings were unexpected (at least before the earlier trial), but in the opinion of the evaluator, the bioequivalence findings are valid. Avoiding this complication may have necessitated the use of Zoladex beyond the usual frequency.

Drug Interactions

No drug interactions studies were submitted with the application.

Pharmacodynamics

No pharmacodynamics studies were submitted with the application.

Efficacy

No new efficacy or safety studies with Pergoveris (fixed dose combination of follitropin alfa (rch) and lutropin alfa (rch)) were submitted in this application since proof of efficacy and safety relied upon data previously approved by the TGA for registration of Luveris (lutropin alfa (rch)). In the Clinical Overview, the sponsor nominated study 6253 - an open, randomised, parallel group dose-finding study of women with primary or secondary anovulation - as the primary efficacy study in the population proposed for the new product.

The clinical evaluator did not re-evaluate those data. However, for completeness, information regarding this study is provided below:

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.

- Participants were randomized to receive no r-hLH or daily doses of 25, 75 or 225 IU, together with 150 IU r-hFSH, both given subcutaneously, for up to 3 treatment cycles.
- Thirty-eight women had 39 first cycles; 10 did not wish to conceive. Five cycles were appropriately excluded from the analysis because of important protocol violations. There were also 9 second cycles and 5 third cycles.
- In the first cycle, 8 women had no r-hLH, 7 had 25 IU, 9 had 75 IU, and 10 women had 225 IU r-hLH.
- 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. For the 34 first cycles, 1/8, 3/7, 5/9 and 5/10 women in the 0, 25, 75 and 225 IU LH groups had at least one large follicle and were given hCG. Zero%, 14.3%, 66.7% and 80.0% for treatment with 0, 25, 75 and 225 IU r-hLH, respectively; satisfied the criteria for "follicular development" (p=0.0124). The study report included cycles cancelled because of OHSS risk as having successful "follicular development" and reported success rates of 0/8, 1/7, 6/9 and 8/10 (0%, 14%, 67% and 80%, p=0.0001 for trend).
- There were three clinical pregnancies in the study, one in the 225 IU LH group (singleton delivery) and two in the 75 IU group (one abortion and one twin delivery).
- The study concluded that in HH women:
    - recombinant r-LH enhances in a dose-dependent manner the ovarian sensitivity to FSH as shown by the proportion of patients developing preovulatory follicles with a fixed dose of FSH administered during a fixed period of time. Both 75 IU and 225 IU r-hLH daily are optimal and similarly effective.
    - recombinant r-LH promotes in a dose-dependent manner E_2 secretion by FSH-stimulated follicles. Based on absolute serum E_2 levels on the day of HCG administration, and endometrium growth during follicular phase, both 75 IU and 225 IU r-hLH daily are optimal and similarly effective.

- recombinant r-LH enhances in a dose-dependent manner development of follicles which are able to undergo adequate luteinisation when exposed to hCG. Both 75 IU and 225 IU r-hLH daily are optimal and similarly effective.

The original evaluator accepted that the study demonstrated an increase in the proportion of first cycles with follicular development and adequate E_2 and P_4 levels with increasing r-hLH doses in association with a fixed dose of r-hFSH, but considered it possible that a higher dose of FSH, instead of the addition of LH, might have a similar effect.

The identification of the 75 IU and 225 IU LH doses as optimal was thought perhaps premature. They produced higher proportions of ovulation outcomes in this study, but 25 IU was enough for one woman and the higher doses were accompanied by higher risks of OHSS and cycle cancellation. The lower dose had a higher rate of cycle cancellation for inadequate follicular development. The study did not demonstrate any advantage of the 225 IU dose over the 75 IU dose, but did not exclude its appropriateness for some women.

Safety

Studies IMP23718 and IMP23722

For Study IMP23722, adverse events (AEs) are shown in Table 3.

Table 3. Adverse events, classified by system organ class (SOC) and preferred term. Study IMP23722.

	Pergoveris (N=73)			Luveris (N=71)		
	Events	Subjects	%†	Events	Subjects	%
Total	193	60	82.2	179	55	77.5
Ear And Labyrinth Disorders*	1	1	1.4	2	2	2.8
Gastrointestinal Disorders	56	35	47.9	21	13	18.3
Abdominal Pain NOS	17	13	17.8	3	2	2.8
Abdominal Pain upper	4	2	2.7	0	0	0.0
Nausea	14	11	15.1	5	4	5.6
General Disorders And Administration Site Conditions	13	10	13.7	19	14	19.7
Injection site bruising	2	2	2.7	1	1	1.4
Injection site erythema	1	1	1.4	0	0	0.0
Injection site oedema				1	1	1.4
Injection site pain	0	0	0.0	4	4	5.6
Injection site paraesthesia	0	0	0.0	1	1	1.4
Immune System Disorders	0	0	0.0	1	1	1.4
Hypersensitivity				1	1	1.4
Infections And Infestations	6	6	8.2	11	10	14.1
Injury, Poisoning And Procedural Complications	5	4	5.5	8	8	11.3
Investigations	0	0	0.0	2	1	1.4
Metabolism and Nutrition Disorders	0	0	0.0	2	2	2.8

	Pergoveris(N=73)			Luveris(N=71)		
Musculoskeletal and Connective Tissue Disorders	8	6	8.2	16	9	12.7
Arthralgia	0	0	0.0	6	3	4.2
Back Pain	7	5	6.8	6	4	5.6
Nervous System Disorders	55	36	49.3	46	26	36.6
Headache NOS	51	34	46.6	42	23	32.4
Psychiatric Disorders	6	5	6.8	7	7	9.9
Renal And Urinary Disorders	1	1	1.4	0	0	0.0
Reproductive System And Breast Disorders	5	5	6.8	8	6	8.5
Respiratory, Thoracic and Mediastinal Disorders	8	6	8.2	8	5	7.0
Cough	1	1	1.4	5	4	5.6
Skin and Subcutaneous Tissue Disorders	5	5	6.8	5	5	7.0
Vascular Disorders	24	22	30.1	23	20	28.2
Hot Flush	24	22	30.1	23	20	28.2

*Note that numbers in SOCs are comprehensive, but only selected preferred terms are listed.

†Per cent of subjects.

Studies submitted previously

In addition to Study 6253 discussed above, Study 6905, which was submitted in the Luveris registration dossier, is considered relevant to the safety assessment. The latter study was similar in design to the former, but enrolled subjects whose LH and FSH were higher than those of study 6253. Forty patients were enrolled.

AEs occurring in > 3% of cycles in Studies 6253 or 6905 are shown in Table 4. At least 1 dose of lutropin alfa was administered in 42 cycles in Study 6253, and 41 cycles in Study 6905.

In Study 6253, 3 patients discontinued because of AEs - all involving symptoms (mild or moderate abdominal pain or enlarged abdomen) and ultrasound scans which were suggestive of OHSS. In study 6905, there were no discontinuations due to AE.

The AE pattern in these studies did not show any association with LH dosage.

Table 4: AEs occurring in > 3% of cycles. Studies 6253 and 6905

Adverse events with total incidence >3 % of cycles*	Lutropin alfa dose (IU/day)	Study 6253	Study 6905
Abdominal pain		2	10
	0		3
	25		3
	75		1
	225	2	3
Anaemia		0	2
	0		1
	75		1
Breast pain		5	0
	0	2	
	25	1	
	75	2	
Dysmenorrhoea			8
	0		3
	25		2
	75		2
	225		1
Dysuria		0	2
	0		1
	25		1
Fatigue			2
	25		1
	75		1
Flatulence			2
	0		1
	225		1
Headache		7	
	0	1	
	25	1	
	75	5	
Hypercholesterolaemia			2
	0		1
	225		1
Injection site reaction			2
	0		1
	25		1
Adverse events with total incidence >3 % of cycles*	Lutropin alfa dose (IU/day)	Study 6253	Study 6905
Nausea		3	4
	25	2	
	75	1	2
	225		2
Ovarian disorder		2	
	75	1	
	225	1	
Pelvic pain		6	
	0	2	
	25	1	
	75	3	
Somnolence		2	
	0	1	
	75	1	
Totals		27	41

*Note that the two studies used different AE dictionaries

Clinical Summary and Conclusions

Two bioequivalence studies were submitted in the dossier (IMP 23718 and IMP 23722) to establish the bioequivalence of the fixed dose combination product with the two individual component products (Gonal-F and Luveris). The clinical evaluator noted that minimal efficacy and safety data were accepted as sufficient for the registration of a product used in a rare condition. Moreover, according to the EU guideline on fixed dose combination product, as the sponsor is requesting a substitution indication, i.e. same indication as for the 2 individual components, in view of simplification of therapy, data requirements are usually pharmacokinetic and occasionally pharmacodynamic if needed. However, this did not imply that the data will necessarily be adequate to justify the registration of a product of convenience (such as the product which is the subject of the present application). In the opinion of the evaluator, the available efficacy and safety data did not fulfil the requirements of the relevant guideline on fixed-combination products (EMEA CHMP/EWP/240/95 1996), which states:

The product should be formulated so that the dose and proportion of each substance present is appropriate for the intended use, and;

The dosage of each substance within the fixed combination must be such as the combination is safe and effective for a significant population subgroup and the benefit/risk assessment of the fixed combination is equal or exceeds the one of each of its substances taken alone.

The evaluator noted that in particular, the proposed dose combination cannot in any way be regarded as standard. The approved PI for Luveris, which has taken into account the results of Study 6253, is not very specific regarding dosage in combination with an FSH preparation, emphasising the need for dose titration in individuals and noting that "A recommended regimen commences at lutropin alfa 75 IU … daily associated with FSH 75 to 150 IU."

V. Pharmacovigilance Findings

No pharmacovigilance data were evaluated with the submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the Delegate's overview and recommendation.

Quality

There were no chemistry or quality control issues that precluded registration.

The Pharmaceutical Subcommittee considered this application at its 126th meeting and concluded that there were no objections on pharmacological and biological grounds to approval.

The evaluator noted that the stability data were acceptable to recommend a shelf life of three years when stored below 25°C and that the product should be protected from light. The proposed finished product specifications were considered acceptable.

Two relative bioavailability studies were submitted. The evaluator concluded that the test product Pergoveris (containing FSH and LH) was bioequivalent to the two reference products Gonal-F (containing FSH) and Luveris (containing LH).

Non-Clinical

There was one additional study that assessed local tolerance of the proposed combination product. No significant effects were observed with the proposed formulation at the proposed strength (single or repeat daily dosing for 7 days) or at 3 times the clinical strength (single dose) in rabbits.

The evaluator recommended approval based on preclinical data.

Clinical

Bioequivalence

Clinical data submitted comprised two bioequivalence studies. Both studies used the formulation of Pergoveris intended for marketing. Bioequivalence was demonstrated in both studies, the first of which compared the bioequivalence of FSH in the fixed dose combination of FSH and LH (Pergoveris) with FSH alone (Gonal-F), and the second of which compared the bioequivalence of LH in the fixed combination product (Pergoveris) vs LH in Luveris.

Efficacy

No new efficacy or safety studies with Pergoveris (fixed dose combination of follitropin alfa (rch) and lutropin alfa (rch)) were submitted in this application since proof of efficacy and safety relied upon data previously approved by the TGA for registration of Luveris (lutropin alfa (rch)). The evaluator noted that two studies were mentioned, studies 6253 and 6905, both of which were evaluated previously. Study 6253 was the primary efficacy study in the population proposed for the new product and this was evaluated in 1999. The study concluded that in hypogonadotrophic hypogonadism (HH), r-hLH enhanced in a dose dependent manner ovarian sensitivity to FSH, E_2 secretion by FSH stimulated follicles and the development of follicles which were able to undergo adequate luteinisation when exposed to hCG. Both regimens of r-hLH (75 IU and 225 IU) were similarly effective and optimal.

The evaluator of that submission, however, was of the opinion that the identification of the two doses of rLH as optimal was premature. More data were required to assert this, as it was not known whether a fixed dose of rLH with ascending doses of FSH could produce similar results. Nevertheless, this study supports the efficacy of two rLH doses (75IU and 225IU) with a fixed dose (150 IU) of FSH. This study does not support a fixed dose combination of Pergoveris.

The evaluator of the current application mentions that the EMEA Guidelines (3CC10a) adopted by the TGA in relation to data requirements in the case of Fixed Dose Combinations state the following:

The product should be formulated so that the dose and proportion of each substance present is appropriate for the intended use. The Delegate has noted that this is not the case as in the treatment for the stimulation of follicular development, doses of r-LH and r-FSH have to be individualised.

The dosage of each substance within the fixed combination must be such as the combination is safe and effective for a significant population subgroup and the benefit/risk assessment of the fixed combination is equal or exceeds the one of each of its substances taken alone. The Delegate has noted that this does not apply in the case of Pergoveris.

The evaluator recommended against registration for the above mentioned indication, the evaluator's reason was that there were no efficacy and safety data submitted with the fixed dose combination, the concern being that "careful attention must be given to the dosage in individual patients, from cycle to cycle". Even with careful monitoring, the risk of ovarian hyperstimulation syndrome (OHSS) is substantial requiring individualisation of doses from cycle to cycle.

Risk-Benefit Analysis

- The Delegate noted that despite the sponsor's objectives of improved convenience and compliance, no data are provided that these goals were met.
- The appropriateness of the dose of individual products included in Pergoveris was stated by the sponsor to be "based on previous experience with LH and FSH". However, the experience to hand submitted to the TGA is as follows: The previous evaluation of Luveris discussed five clinical efficacy studies where a total of 170 females were recruited. Dosage of r-FSH was standardised to 150 IU daily and the evaluator conceded that "to identify that 75IU and 225 IU

LH doses as optimal is perhaps premature". This was relating to Study GF 6253. Similar comments were expressed regarding other studies. The overall conclusion was that the optimal starting dose of rFSH was 75IU and that re LH it was less clear. This would not support the fixed dose combination of Pergoveris.

- The sponsor has discussed two previously evaluated studies- 6253 and 6905, to support the use of LH and FSH. The efficacy of combination of LH and FSH is not disputed in the treatment of HH. It is the safety and efficacy of the fixed dose combination that is of concern to the evaluator.
- It was stated by the sponsor that the ratio of 150 IU of FSH and 75 IU of LH has been shown to be safe and effective in most patients with HH. If the dose of either r-hFSH or r-hLH needs to be increased, or a lower dose of either component is required to commence treatment, it is possible to use the individual injection. Clearly, if this is the case, it defeats the purpose of having a fixed dose combination.
- In relation to safety, the sponsor concluded that the clinical studies with Pergoveris, Luveris and the post market experience support an acceptable safety profile. It was stated in response to the clinical evaluation report, that since market authorisation of Pergoveris in June 2007, there had been no serious events. The Delegate noted that the numbers involved in this rare disease may not signal concern; and that in the original application to register Luveris, there were 7 reports of OHSS, of which 6 were in those who had 75IU rLH. These were classified as serious adverse events in the clinical trials. The Delegate requested that the sponsor should state the number of cases of OHSS that were reported in the PSURS, in its pre-ADEC response.

The Delegate agreed with the evaluator that the efficacy and safety of this product had not been satisfactorily established. The concern was that this indication requires the need to individualise both r-LH and r FSH in order that the occurrence of OHSS is minimised; in relation to Luveris, the studies did show that 37.5IU of r-LH could be effective. Based on those studies, it could be predicted that an additional dose of FSH needed to be given in a clinical setting to optimise follicular development in the target population. Thus, this approach to treatment defeated the purpose of a fixed dose combination.

The Delegate recommended that should the advisory committee recommend approval of this application, the indication should mirror that approved for Luveris which is;

Luveris 75 IU in association with a recombinant follicle stimulating hormone (FSH) preparation is recommended 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 < 1.2 IU/L.

The main comments from the sponsor's response were as follows:

By combining two gonadotrophins registered for co-administration as separate injections, Pergoveris reduces the number of daily injections from two to just one. Over a single treatment cycle that can range up to 5 weeks this represents a substantial decrease in patient burden. Pergoveris is not proposed as the sole option for treating HH but represents a convenient, safe and effective therapy in this diverse population of anovulatory patients.

The FSH dose of 75 IU was not studied in the Luveris registration trials. With respect to LH none of the patients received a dose of 37.5 IU. Although a few patients at the minimal dose of 25 IU LH met the primary endpoint of follicular development, none achieved pregnancy due to inadequate endometrial development to support embryo implantation and pregnancy. The pivotal Luveris registration study confirming the r-hLH dose of 75IU was Study 6253; the results of this study were supported by Study 6905. The percentage of patients fulfilling all three criteria that defined the

primary endpoint, follicular development, and the clinical pregnancy rates (secondary endpoint) are presented in Table 5.

Table 5: Follicular development and Clinical Pregnancy results in Study 6253 and 6905

Study	**6253 (LH <1.2 IU/L)**		**6905 (LH <1.2 IU/L Subset)**	
Patients	n=34		n=15	
Endpoints	Follicular Dev. (cycle A)	Clinical Pregnancy	Follicular Dev. (cycle A)	Clinical Pregnancy
r-hLH Treatment:				
225 IU/day	8/10 (80%)	1/8 (12.5%)	3/4 (75%)	2/4 (50%)
75 IU/day	6/9 (67%)	2/10 (20%)	2/3 (67%)	1/3 (33.3%)
25 IU/day	1/7 (14%)	0/8 (0%)	5/5 (100%)	0/5 (0%)
0 IU/day	0/8 (0 %)	0/8 (0%)	0/3 (0%)	0/3 (0%)

A statistically significant dose-response relationship between follicular development and the administered r-hLH dose was observed in Study 6253 (p=0.0001). In Study 6905, a subpopulation analysis of patients with basal LH levels <1.2 IU/L (as defined in 6253) demonstrated that among the three individual components of follicular development a dose-related, statistically significant trend was observed in the proportion of patients with pre-ovulatory E_2 levels ≥160 pg/mL (p=0.039).

In relation to occurrence of OHSS in the Luveris registration trials, there was no evidence of any significant relationship between the dose of r-hLH and the occurrence of OHSS.

Since the first launch of Pergoveris worldwide, one Individual Case Safety Report (ICSR) involving OHSS was reported to the company from 2-years post-marketing setting. Comparatively, since European approval of Luveris on 29 November 2000 (International birth date or IBD), a total of 15 ICSRs were reported to the Company for a total patient's estimate of 160,800 treatment-cycles over the period from IBD to 28 November 2008. Among these reports, 3 spontaneous reports of serious OHSS were received. Two of them were observed in patients who received Luveris (75 IU/d over 7 and 8 days respectively) in combination with GONAL-f for ovulation induction and one after administration of the combined drugs (150 IU/d of Luveris) for ART.

With respect to the risk of the development of OHSS and multiple pregnancy, it is current practice for the physician to assess the potential risk of OHSS before administering hCG. The decision not to administer hCG is based on a clinical judgement and it is extremely rare for patients to develop OHSS if hCG is not administered. This clinical judgement is supported by guidelines from professional medical societies such as the Royal College of Obstetricians and Gynaecologists and the American Society of Reproductive Medicine. Furthermore, the proposed PI highlights conditions under which OHSS is likely to occur and cautions the physician to withhold hCG administration in such circumstances.

The overview of safety data does not show any new significant safety findings related to Pergoveris, nor unexpected adverse events associated with the combination of r-hFSH and r-hLH, thus confirming a positive benefit/risk balance of Pergoveris in the proposed hypogonadotropic hypogonadism indication.

Evaluation Committee

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations, the Delegate's overview and the sponsor's responses, recommended approval of the application for the following indication:

Pergoveris is recommended 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 < 1.2 IU/L.

The Committee agreed that a dose response relationship for lutropin was not well defined and that doses of both lutenising and follicle stimulating hormone must be individualised according to response and tolerability. However the combination was considered approvable as the indication proposed by the sponsor was amended as suggested by the Delegate to limit use to patients whose endogenous serum LH levels are less than 1.2 IU/L. This limitation would exclude use of Pergoveris in patients with polycystic ovarian disease who are known to be at higher risk of developing ovarian hyperstimulation syndrome.

Outcome

Based on review of quality, safety and efficacy data, TGA approved the registration of the new fixed dose combination product Pergoveris containing follitropin alfa (rch)/lutropin alfa (rch) (Pergoveris) powder for injection 150 IU / 75 IU for the indication:

> *Pergoveris is recommended 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 < 1.2 IU/L.*

Attachment 1. Product Information

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

NAME OF THE 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 ß-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 ß-subunit is formed by 111 amino acids carrying two carbohydrate moieties linked to Asn-7 and Asn-24 and containing six disulphide bonds. CAS-146479-72-3 (follitropin alfa, (rch).

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

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.

PHARMACOLOGY

Pharmacodynamics

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 around10-14 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.

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 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

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**					
Study	GF 6253	21008	GF 6905	Total no LH	GF 6253	2100 8	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
Miscarriages	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

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.

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 and pituitary gland
- ovarian enlargement or cyst not due to polycystic ovarian disease
- gynaecological haemorrhages of unknown origin
- pregnancy and lactation

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 generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with gonadotrophins may further increase the risk. 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.

Interactions with other drugs

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

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	≥ 1/10
Common	1/100 - 1/10
Uncommon	1/1000 - 1/100
Rare	1/10 000 - 1/ 1000
Very Rare	≤ 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, 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, bloating, 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 of asthma

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

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.

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.

PRESENTATION AND STORAGE CONDITIONS

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.

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

NAME AND ADDRESS OF THE SPONSOR

Supplied in Australia by:

Merck Serono Australia Pty Ltd

3-4/25 Frenchs Forest Road

Frenchs Forest NSW 2086

Supplied in New Zealand by:

Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks, Auckland

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

TGA approved: 10 November 2009

® Registered Trade Mark

A001-1109