PUBLIC SUMMARY DOCUMENT

Product: FOLLITROPIN ALFA AND LUTROPIN ALFA, injection, 150 IU + 75 IU, Pergoveris®
Sponsor: Merck Serono Australia Pty Ltd
Date of PBAC Consideration: March 2014

1. Purpose of Application

The resubmission requested PBS listing on the Section 100 In-Vitro Fertilisation and Gamete Intra-fallopian Transfer (IVF/GIFT) Program for the treatment of patients who are receiving medical treatment as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule and who have severe luteinising hormone (LH) deficiency.

2. Background

This was the first major PBAC submission for follitropin alfa 150 IU + lutropin alfa 75 IU. A minor submission was previously considered by the PBAC at its March 2012 Meeting.

At the March 2012 meeting, the PBAC noted that no evidence was presented in the submission that could be used to determine the comparative effectiveness of the combination product and follitropin alfa. Additionally, inadequate evidence was provided of the efficacy of the combination product in the defined sub-group of patients with severe LH and follicle stimulating hormone (FSH) deficiency. At the time, the PBAC considered that these issues would need to be addressed in a major submission to allow full evaluation of the clinical data. The PBAC rejected the submission on the basis of inadequate clinical evidence of comparative effectiveness.

3. Registration Status

Pergoveris was TGA registered on 19 November 2009 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. Listing Requested and PBAC's View

Section 100 (IVF/GIFT treatment)

Patients who are receiving treatment as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule and who have severe LH deficiency.

The submission proposed that the cost of this follitropin alfa + lutropin alfa fixed dose combination (FDC) product will be cost-minimised to recombinant follicle stimulating hormone (rFSH) alone, with the cost of the recombinant LH (rLH) component to be covered by the sponsor at no additional cost to the Government.

A formal cost-minimisation analysis for the comparison between follitropin alfa + lutropin alfa and its individual components administered concomitantly was not presented in the submission.

5. Clinical Place for the Proposed Therapy

The PBAC noted that in women for whom exogenous FSH therapy is indicated as part of a Controlled Ovarian Stimulation (COS) regimen, no exogenous administration of LH was needed to achieve successful follicular development because these women already have adequate endogenous levels of LH.

Some patients who have hypogonadotropic hypogonadism (HH) or who experience profound pituitary down-regulation, do not have adequate levels of endogenous LH that is required to achieve optimal follicular development and steroidogenesis.

The submission stated that women with severe LH deficiency who wish to become pregnant are currently treated with follitropin alfa supplemented with lutropin alfa. If follitropin alfa + lutropin alfa becomes listed, patients will be treated with one daily injection of follitropin alfa + lutropin alfa instead of follitropin alfa and lutropin alfa administered as two separate injections. The submission noted that available IVF treatment regimens in Australia vary and detailed treatment algorithms were not presented.

6. Comparator

The submission nominated follitropin alfa, one component of the FDC product, as the main comparator. The PBAC noted the second component of the FDC product, lutropin alfa (a recombinant luteinising hormone rLH), is registered by the TGA but not listed on the PBS and is not administered on its own.

The submission also considered human menopausal gonadotropin (hMG) as an additional but minor comparator.

In its Pre-Sub-Committee Response (PSCR), the sponsor stated that "the clinical comparisons of Pergoveris against its two components were not required for the registration approval of Pergoveris and have not been conducted".

The PSCR claimed that two cross-over studies were presented to the TGA for the registration of follitropin alfa + lutropin alfa FDC. The PSCR claimed that the two studies showed that when administered together in the same injection, rFSH and rLH have the same pharmacokinetic profile, and therefore provide equivalent activity to the components given as separate injections. The PBAC noted that the doses of FSH (300 IU and 900 IU) and LH (150 IU and 450 IU) used in the studies were not the doses in the current fixed-dose formulation for which listing is sought (FSH: 150 IU; LH: 75 IU).

The PBAC considered that in clinical practice, patients who have severe LH deficiency would be taking LH in addition to FSH. Thus, the relevant comparator for this population would be LH and FSH given concomitantly.

7. Clinical Trials

The submission presented the following clinical trials:

a) Three dose ranging studies (Studies 6253, 6905, and 7798) comparing different doses of rLH (ranging from 25IU to 225IU, including 75IU) in concomitant combination with rFSH 150IU versus rFSH 150IU alone;
b) A placebo controlled trial (Study 21008) and its extension phase comparing the concomitant administration of rLH 75IU and rFSH 150IU with rFSH 150IU alone; and
c) Three studies comparing follitropin alfa + lutropin alfa (rLH 75IU: rFSH 150IU) with gonadotrophin-menopausal human (hMG 150IU in the Carone studies and hMG 225IU in the Pacchiarotti study).

The PBAC noted that there were no studies of the follitropin alfa + lutropin alfa FDC, versus the concomitant administration of the components (rFSH 150 IU and rLH 75 IU). Trials 6905 and 7798 presented in the submission were of small sizes and did not provide relevant comparisons.

The published trials and associated reports presented in the submission are shown in the following table:

Trials and associated reports presented in the submission. *Bolded studies considered key for the evaluation.*

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials:		
rLH 75IU + rFSH 150IU versus rFSH 150IU + placebo		
6253	An open-label, randomised, dose-finding, multicentre, pivotal study to determine the minimal effective dose and assess the safety of recombinant Human Luteinising Hormone (rLH) to support recombinant human Follicle Stimulating Hormone (rFSH)-induced follicular development in LH and FSH deficient anovulatory women.	1998
Loumaye, E.	Recombinant Human Luteinizing Hormone (LH) to Support Recombinant Human Follicle-Stimulating Hormone (FSH)-Induced Follicular Development in LH- and FSH-Deficient Anovulatory Women: A Dose-Finding Study.	*Journal of Clinical Endocrinology and Metabolism*, 1998;83:1507-1514
21008	A Phase III, prospective, randomized, controlled, double-blind, multicenter study to confirm the efficacy and safety of recombinant human Luteinizing Hormone (r-hLH), 75IU, administered subcutaneously, to support recombinant human Follicle Stimulating Hormone (r-hFSH)-induced follicular development in women with hypogonadotropic hypogonadism and severe LH deficiency who desire pregnancy.	2001
Shoham, Z et al	Recombinant LH (lutropin alfa) for the treatment of hypogonadotrophic women with profound LH deficiency: a randomized, double-blind, placebo-controlled, proof-of-efficacy study.	*Clinical Endocrinology,* 2008;69: 471-478
Kaufmann, R *et al*.	Recombinant human luteinizing hormone, lutropin alfa, for the induction of follicular development and pregnancy in profoundly gonadotrophin-deficient women.	*Clinical Endocrinology*, 2007;67:563-569
6905	An open, randomized, dose-finding, multicenter study to determine the minimal effective dose and to assess the safety of recombinant-human Luteinizing Hormone (r-hLH) to support recombinant-human Follicle	1999

	Stimulating Hormone (r-hFSH)-induced follicular development in anovulatory women with hypogonadotropic hypogonadism.	
O'Dea, L et al	Recombinant LH in Support of Recombinant FSH in Female Hypogonadotropic Hypogonadism - Evidence of Threshold Effect.	*Fertility and sterility* 2000; 74 (3 Suppl 1):S36
O'Dea L et al.	Follicular development induced by recombinant luteinizing hormone (LH) and follicle stimulating hormone (FSH) in anovulatory women with LH and FSH deficiency: evidence of a threshold effect	*Current Medical Research and Opinion* 2008; 24 (10):2785-2793
Pergoveris® versus Menopur		
Pacchiarotti, A et al	Urinary hMG (Menopur) versus recombinant FSH plus recombinant LH (Pergoveris®) in IVF: a multicenter, prospective, randomized controlled trial.	*Fertility and sterility*, 2010; 94 (6): 2467-2469.
Carone, D et al	Clinical outcomes of ovulation induction in WHO group i anovulatory women using r-hFSH + r-hLH in a 2:1 ratio compared to hMG.	*Human Reproduction*, 2010; 25 S1: i312. Abstract P508 of the 26th Annual Meeting of the European Society of Human Reproduction and Embryology, Rome, Italy, 27-30, June 2010.
Carone, D et al	Efficacy of different gonadotropin combinations to support ovulation induction in WHO type I anovulation infertility: Clinical evidences of human recombinant FSH/human recombinant LH in a 2:1 ratio and highly purified human menopausal gonadotropin stimulation protocols.	*Journal of Endocrinological Investigation,* 2012; 35 (11): Abstract presented.

Observational studies		
Burgués, S et al	The effectiveness and safety of recombinant human LH to support follicular development induced by recombinant human FSH in WHO group I anovulation: Evidence from a multicentre study in Spain.	*Human Reproduction*, 2001; 16 (12): 2525-2532.
Harbulak, P et al	Controlled ovarian stimulation using a novel 2:1 FSH: LH gonadotrophin preparation – results from routine clinical practice.	*Journal für reproduktionsmedizin und endokrinologie*, 2010; 7(4):298, Abstract M-019.
Bioequivalence study		
Picard, M et a;	Bioequivalence of recombinant human FSH and recombinant human LH in a fixed 2:1 combination: two phase I, randomised, crossover studies.	*Current medical research and opinion*, 2008; 24(4):1199-1208.

The summary of the key features of the included evidence are shown in the table below.

Key features of the included evidence

Study/Study details	Concomitant rLH 75 IU + rFSH 150 IU vs. rFSH 150 IU		Pergoveris® (225 IU) vs. Menopur® (225 IU)	Pergoveris studies cited in PSCR	
	6253(1998)	21008(2001)	Pacchiarotti et al. (2010)	Buhler & Naether (2010)	Buhler & Fischer (2011)
Trial design	R, OL, parallel group, dose finding	R, DB, placebo controlled	R, DB	Observational	Observational, matched case-control
Median treatment duration (days) [◊]	14	12	14 for Menopur 11 for Pergoveris	11	FSH + LH: 10.8 hMG: 10.7
Number of subjects	38[§]	39	122	857	1,573
Total cycles	53	39	Not stated	919	Not stated
Daily treatment regimens (IU)	FSH: 150 IU LH: 0, 25, 75 or 225 IU	FSH: 150 IU + LH: 75 IU vs. FSH: 150 IU + placebo	Mean daily doses: Pergoveris: 440 IU Menopur: 250 IU	Mean daily dose of Pergoveris: 245 IU	Exact doses not stated FSH + LH (in a 2:1 ratio), hMG, hMG + FSH
Patient population in terms of baseline LH, IU/L	<1.2	<1.2	<1.2	21% of subjects had LH deficiency	Not stated
Primary outcome(s)	Composite[Δ,*]	Composite[Δ,*]	Number of oocytes[#] Pregnancy rate/cycle[#]	Number of oocytes retrieved, Number of embryos transferred, Pregnancies	Clinical pregnancy rate, Implantation rate per embryo transferred
Risk of bias	High	High	High	Not evaluated	Not evaluated

§Primary efficacy analysis was conducted on 34 patients. Patients were randomised to receive 0, 25, 75 or 225 IU

[Δ]Three criteria: ≥1 follicle with a diameter of ≥17mm; and pre-ovulatory mean serum E2 level of ≥400 pmol/L (109 pg/mL) on the day of hCG administration; and mid-luteal phase P4 level of ≥25 nmol/L (7.9 ng/mL);

[◊]Study 6253: According to protocol, each patient was to be treated for one cycle (Cycle A). If consenting however, patients could be treated for a further one or two cycles (Cycle B /C). Study 21008: Only one cycle permitted (Cycle A).

[*]Also considered pregnancy rates but results unreliable due to small number of events.

[#]Not specified in study as primary outcome but included as an outcome along with others.

IU=International units; rLH=Recombinant Human Luteinizing Hormone; rFSH= Recombinant Human Follicle-Stimulating Hormone; DB=double blind; OL=open label; R=randomised

Source: Compiled during the evaluation

The PBAC considered Studies 6253, 21008 and Pacchiarotti et al (2010) as the best available evidence presented in the submission, noting that there were some flaws with these studies.

The Pacchiarotti et al study compared follitropin alfa + lutropin alfa with hMG. Although a cost-minimisation comparison between these products was not proposed in the submission, the PBAC considered this comparison useful. Studies 6253 and 21008 compared the concomitant administration of rLH 75IU and rFSH 150IU with rFSH 150IU alone.

The PBAC noted and welcomed the input from healthcare professionals (7) via the consumer comments facility on the PBS website. The sponsor did not request a hearing for this item.

8. Results of Trials

The PBAC noted the primary outcome measured in Trials 6253 and 21008 was a composite outcome of whether a patient had the following:

- one or more follicles with a diameter of 17 mm or greater; and
- pre-ovulatory mean serum oestradiol, (E2) level of 400 pmol/L (109 pg/mL) or greater on the day of human chorionic gonadotrophin (hCG) administration; and
- mid-luteal phase progesterone, P4 level of 25 nmol/L (7.9 ng/mL) or greater.

The submission presented additional analyses that defined over-response or over-stimulation as a "success" in terms of treatment effect. In Trial 21008, a patient was considered to be at risk of developing ovarian hyper-stimulation syndrome (OHSS) if serum E2 concentrations increased rapidly and/or there was an excessive number of growing follicles visualised. In this study protocol, risk of OHSS was based on more than 3 follicles measuring 15 mm or more and/or serum E2 of 1100 pg/mL or greater. If this occurred in a cycle, hCG was withheld and the cycle cancelled. The PBAC agreed with the Economics Sub-Committee (ESC) that this analysis may have actually equalled ovarian hyper-stimulation syndrome (OHSS) events.

In Pacchiarotti et al. (2010), the primary outcome measure was not stated but included the number of oocytes retrieved and pregnancy rate/cycle. The PBAC considered that this study suggested a higher risk of OHSS associated with follitropin alfa + lutropin alfa FDC and more mature oocytes retrieved from patients treated with hMG.

A summary table of efficacy outcome measures and results across the studies are presented below.

Summary of efficacy outcome measures and results across the studies

Study/Efficacy outcome measure	**rFSH 150 IU vs. concomitant rLH 75 IU + rFSH 150 IU**		**Pergoveris® 225 IU vs. Menopur® 225 IU**	***Pergoveris studies cited in PSCR***	
	6253(1998)	**21008(2001)**	**Pacchiarotti (2010)**	***Buhler & Naether (2010)***	***Buhler & Fischer (2011)***
Composite outcome^ of: 1 or more follicles with a diameter of 17mm or greater; and pre-ovulatory mean serum E2 level of 400 pmol/L (109 pg/mL) or greater on the day of hCG administration; and mid-luteal phase P4 level of 25 nmol/L (7.9 ng/mL) or greater;	0/8 (0.0%) vs. 4/9 (44.5%)	1/13 (7.7%) vs. 11/26 (42.3%)	NR	*NR*	*NR*
Relative risk (RR)	*Not calculated*	*5.50# (1.19, 25.48), p=0.033*			

Risk difference(RD) (95% CI) p-value NNT (95%CI)	*0.44[#] (0.03, 0.86)* *p=0.0824*	*0.35[#] (0.03, 0.66)* *p-value not stated* *3 (2, 29)*			
Live birth	NR	NR	NR	*NR*	*NR*
Clinical pregnancy rate per cycle	16.6% vs. 0%	ITT population[β],(N= 39): 7.7% vs. 3.8% Evaluable population[β],(N= 34): 10% vs. 4.2%	Pergoveris: 28.3% (15/53) Menopur: 29.3% (17/58)	*Pergoveris: 22%*	*Pergoveris: 25.5%* *Menopur:21.5 %*
Relative risk (RR)	*Not calculable (0 events)*	*1.0 (0.1, 10.0)* *0.4 (0.0, 5.9)*	NR	*NA*	*NR*
Risk difference (RD)	*0.17 (-0.11, 0.44) p=0.49*	*0 (-0.2, 0.2)* *-5.8 (-0.2, 0.1)*	NR	*NA*	*NR*
Total oocytes retrieved ± (SD)	NR	NR	Pergoveris: 7.8 (1.1) Menopur: 4.1 (1.2)	*Pergoveris: 8.6 (5.6)*	*Pergoveris: 9.0 (5.8)* *Menopur: 7.8 (5.4)*

NR – not reported; NA – not applicable;
^ Based on not counting patients at risk of OHSS as a 'success' in terms of treatment effect
[β]ITT population included all patients who received at least one injection of randomized treatment and who had at least one assessment after initiation of treatment. Only 3 patients in the placebo arm and 13 patients in the LH 75IU arm received human chorionic gonadotropin. If these are the assumed denominators for pregnancy rates, then the proportions in the placebo and LH 75 arms are 33.3% (1/3) and 15.4% (2/13), respectively. Evaluable population consisted of patients who did not have major deviations from eligibility or treatment plan, or patients who were non-evaluable for the primary efficacy endpoint (see Section 16.1.9 of the CSR for further details).
[#] *Calculations in italics conducted during the evaluation using Fisher's exact test in STATA.*
Outcomes from Buhler & Naether (2010) and Buhler & Fischer (2011) compiled by the ESC.

The PBAC noted that in Study 6253, the results favoured any rLH-containing treatment arm compared with the treatment arm without rLH (0 IU). The addition of 75 IU of rLH to 150 IU of rFSH resulted in a statistically significant difference favouring the combination. The difference in the proportion of clinical pregnancies/initiated cycle between the 75 IU and 0 IU rLH treatment arms was not statistically significant (0.17; 95%CI:-0.11, 0.44).

The PBAC noted that in Study 21008, there was a statistically significant increase in the proportion of patients meeting the composite outcome from the addition of rLH 75IU to rFSH 150 IU in the ITT population. In terms of the outcome of pregnancy rates, there was a higher proportion of clinical pregnancies in the placebo group (rFSH 150 IU alone) compared to the concomitant administration of rLH75 IU + rFSH 150IU.

The PBAC noted that Pacchiarotti et al 2010 presented results showing statistically significant differences between hMG versus follitropin alfa + lutropin alfa FDC in terms of the total number of oocytes retrieved (4.1 ±1.2 vs. 7.8 ±1.1), mature oocytes retrieved (48.2% vs. 34.7%), days of stimulation (14.1±1.6 vs. 10.9 ±1.1), total units of FSH administered (3,525 ±232.5 vs. 4,800 ±345) and the proportion of cancelled patients for high risk of OHSS (1.7% vs. 13.2%). The PBAC noted that the proportion of mature oocytes retrieved was higher for the hMG arm

Overall, the PBAC considered that the trials presented did not assess the comparative effectiveness of follitropin alfa + lutropin alfa for the patient-relevant outcome of pregnancy or live births. The PBAC considered that the small study sample sizes made the data difficult to interpret, but noted that in some of the trials the results favoured the control arm over follitropin alfa + lutropin alfa (higher proportion of clinical pregnancies in the placebo group in Study 21008, more mature oocytes retrieved for the hMG arm in Pacchiarotti et al 2010).

With regard to comparative harms, the PBAC noted that the results presented different number of cycles across treatment arms thus making the comparative safety data difficult to interpret. Multiple cycles of the same dose of rLH for example, may or may not result in more adverse events (AEs) compared to fewer cycles of another dose.

The PBAC noted in Study 6253, a total of 42 adverse events were reported in 14 (26.4%) of the 53 cycles. 26.2% occurred in cycles treated with rLH and 27.2% in cycles not treated with rLH. The most frequent adverse events included headache, pelvic pain and breast pain. The submission noted that three patients from one centre, treated with 0, 25 and 75 IU rLH, accounted for 27 of the 42 adverse events. No local reaction or only a mild reaction was reported in 95.6% of injections of rLH and 96.3% of injections of rFSH. There were no data from this trial to directly assess the comparative safety per cycle of follitropin alfa + lutropin alfa FDC versus the rFSH component alone.

Overall, there was no association between rLH dose and the incidence or type of adverse events as multiple cycles of the same dose of rLH may or may not have resulted in more adverse events compared to fewer cycles of another dose. The PBAC therefore considered it difficult to interpret the comparative safety data.

The PBAC noted that in Study 21008, a total of 44 events were recorded in 13 patients (33.3%). 27 of these events occurred in 9 patients (33.3%) in the rLH group, and 17 events occurred in 4 patients (33.3%) in the placebo group. The most frequently reported adverse event (occurring in 2 or more patients) was abdominal pain, flatulence, nausea, headache, injection site reaction, and ovarian cysts. The proportion of patients with gastrointestinal disorders was slightly higher in the 75 IU rLH +150 IU rFSH (24%) group vs. the rFSH + placebo group (17%). The majority of adverse events were judged by the investigator to be mild or moderate in severity. One event in the placebo group was judged to be severe OHSS (the patient was pregnant). There were no deaths in the study. There were no data from this trial to directly assess the comparative safety of follitropin alfa + lutropin alfa FDC versus the rFSH component.

The PBAC recalled its previous concerns regarding ovarian hyper-stimulation syndrome (OHSS) in the general context of assisted reproductive therapy. The ESC had compiled the table below comparing OHSS rates across the studies.

Summary of safety measures and results across the studies

Study/safety measure	rFSH 150 IU vs. concomitant rLH 75 IU + rFSH 150 IU		Pergoveris® 225 IU vs. Menopur® 225 IU	*Pergoveris studies cited in PSCR*	
	6253(1998)	21008(2001)	Pacchiarotti (2010)*	*Buhler & Naether (2010)*	*Buhler & Fischer (2011)*
OHSS	0/11 (0%) vs. 2/53 (3.8%)	1/12 (8.3%) vs. 0/27 (0%)	7/53 (13.2%) vs. 1/58 (1.7%)	*0.3%*	*NR*
Relative risk	Not stated	Not stated	*7.66 (1.38, 42.59), p=0.0266*	Not stated	Not stated
Risk difference	Not stated	Not stated	*0.11 (0.02, 0.21)*	Not stated	Not stated
NNH	Not stated	Not stated	*9 (8, 50)*[β]	Not stated	Not stated

OHSS = Ovarian hyper-stimulation syndrome, NNH = number needed to harm
[β]NNH = One in 9 patients will cancel the cycle due to a high risk of ovarian hyper-stimulation syndrome (OHSS) if treated with Pergoveris® rather than with Menopur®.
* Cycle cancellation due to risk of OHSS.
Source: Compiled during the evaluation. Study 6253 OHSS figures from Table B.6.13, p.54 of the Commentary, 'Ovarian disorder' row, Study 21008 OHSS figures from Table B.6.14, p.55 of the Commentary, Pacchiarotti et al. (2010), Buhler & Naether (2010) and Buhler & Fischer (2011) OHSS figures from Table 1, p.5 of the PSCR.

The following table presents results for the proportion of "cancelled patients for high risk of OHSS" from Pachiarotti et al.

Proportion of cancelled patients for high risk of OHSS (N=111)

Treatment arm	n/N(%)	Difference in proportion vs control (95% CI)	Relative Risk (RR), (95% CI), p-value	NNT(95% CI)
Control arm: 225IU Menopur®	1/58 (1.7%)	0.11 (0.02, 0.21)	7.66 (1.38, 42.59), p=0.0266	9 (8, 50)
Pergoveris® 225IU	7/53 (13.2 %)			

Source: Compiled during the evaluation

The PBAC expressed concern regarding the statistically significantly higher proportion of cancelled cycles due to high risk of OHSS in the follitropin alfa + lutropin alfa arm compared to the hMG arm. The PBAC considered that, although the absolute numbers of cycles cancelled were small (1/58 (1.7%) for hMG vs. 7/53 (13.2%) for follitropin alfa + lutropin alfa), this was a potential safety concern. The PBAC noted that on the basis of these data, one in nine patients will cancel the cycle due to a high risk of OHSS if treated with follitropin alfa + lutropin alfa compared to hMG. "

9. Clinical Claim

The submission claimed that LH and FSH, when given concomitantly, were superior to FSH administered alone in women with LH deficiency.

The PBAC noted that this superiority claim related only to the surrogate endpoint of follicular stimulation (or overstimulation) rather than for pregnancy outcomes.

The PBAC considered that the comparative safety of follitropin alfa +lutropin alfa was a concern, particularly the risk of OHSS.

10. Economic Analysis

The submission proposed that the cost of follitropin alfa + lutropin alfa FDC will be the same as the cost of rFSH alone, with the cost of the rLH component to be covered by the sponsor at no additional cost to Government.

A formal cost-minimisation analysis for the comparison between Pergoveris and its individual components administered concomitantly was not presented in the submission.

The PBAC considered that a cost-minimisation approach would be reasonable only when the efficacy and safety of follitropin alfa + lutropin alfa FDC are non-inferior to rFSH and rLH administered concomitantly in the population with severe LH deficiency. However, the submission did not present clinical data for this comparison.

The submission did not provide an economic evaluation for the comparison between follitropin alfa + lutropin alfa FDC and hMG.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net nil cost per year to the PBS.
The PBAC considered that there may be potential for market growth given the potential attraction to patients of reduced injections, and because the market could expand into the patient group that is currently paying privately for rLH.

The PBAC noted the practical issues in clinical practice that would be caused by the absence of a single-component product of rLH, particularly as the Product Information for the FDC products directs prescribers to titrate dose according to individual response. The PBAC also noted that in relation to fixed dose combination products, the PBAC Guidelines (PT1.1 Additional information requests to support listing of fixed combination products, page 266), states that an FDC product should not result in inappropriate dosing of either component (e.g. should not contain components for which individual dose titration is preferable). While noting the PSCR's claim that a majority of patients do not require dose titration, the PBAC nonetheless considered that the absence of both components of the FDC as separate products was an issue.

12. PBAC Outcome

The PBAC rejected the submission to list follitropin alfa + lutropin alfa FDC on the Section 100 IVF/GIFT Programme. The PBAC considered that the submission had not established the comparative effectiveness and safety of the FDC to either follitropin alfa given alone or the components – follitropin alfa and lutropin alfa – given separately or other products containing human menopausal gonadotrophin.

The PBAC did not agree that the correct comparator was follitropin alfa. The PBAC considered that the comparator should include both FSH and LH.

The PBAC considered that the clinical evidence presented in the submission was not informative, noting the small study sample sizes and lack of data on the effect of treatment on pregnancy rates. The PBAC did not consider that the evidence provided for the surrogate endpoint of follicular stimulation (or overstimulation) was adequate. The PBAC also noted that some of the data presented appeared to favour the control treatments.

The PBAC considered that the comparative safety of follitropin alfa +lutropin alfa was a concern, particularly the risk of OHSS.

The PBAC noted that the submission did not present a formal cost-minimisation analysis, and considered that an appropriate cost-minimisation would need to compare follitropin alfa +lutropin alfa FDC with the components administered concomitantly.

The PBAC considered that the absence of rLH in a single-component product was a concern, noting that it would complicate dose titration in clinical practice.

Recommendation:
Rejected

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Merck Serono is disappointed with the PBAC rejection. The PBAC focussed its recommendation from the Pacchiarotti (2010) study which used a secondary comparator and which is not indicative of Australian clinical practice because patients received almost 3 times the appropriate dose of FSH/LH. Pergoveris has been available in most OECD markets since 2009, and has been successfully used to increase the chance of pregnancy in these women without significantly increasing the risk of OHSS. As noted in our pre-PBAC response, the updated PSUR demonstrated that there were no new findings bearing on the established overall safety profile of Pergoveris. We also noted the feedback from healthcare professionals in the public consultation process that Pergoveris would be beneficial.

Merck Serono is confident that Pergoveris will benefit Australian women with severe LH deficiency and will continue to work with the PBAC to find a way forward.