PUBLIC SUMMARY DOCUMENT

Product: Corifollitropin alfa, solution for injection, 150 microgram in 0.5 mL pre-filled syringe, Elonva ®
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application

1) To request the current Section 100 IVF/GIFT Program listing to include treatment of women who weigh over 90 kg; and
2) To review the therapeutic relativity and price of corifollitropin alfa 150 micrograms/0.5 mL compared to conventional recombinant follicle stimulating hormone (rFSH) in light of new trial evidence.

2. Background

At its July 2011 meeting, the PBAC recommended listing for corifollitropin alfa under the Section 100 IVF/GIFT treatment program for patients receiving assisted reproductive technologies and who have an antral follicle count of 20 or less, weigh 90 kg or less and are undergoing a gonadotrophin releasing hormone antagonist cycle. The PBAC recommended listing on the basis of cost-minimisation to follitropin beta (rFSH).

A copy of the Public Summary Document from the July 2011 meeting is available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-corifollitropic-july11.

3. Registration Status

Corifollitropin was TGA registered on 30 July 2010 for controlled ovarian stimulation (COS) for the development of multiple follicles and pregnancy in women undergoing in-vitro fertilisation techniques.

4. Listing Requested and PBAC's View

Section 100 (IVF/GIFT treatment)

A patient who is receiving treatment as described in items 13200, 13201 or 13202 of the Medicare Benefits Schedule and who:

(i) Has an antral follicle count of 20 or less; and
(ii) Is undergoing a gonadotrophin releasing hormone antagonist cycle

Note:
Supply of these items is through an accredited IVF/GIFT clinic. For enquiries relating to the IVF/GIIFT Program, medical practitioners should contact Medicare Australia on 1800 700 270.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Several different protocols exist for controlled ovarian stimulation for ART using different combinations of drug treatments. During controlled ovarian stimulation, rFSH was administered to stimulate follicular development. rFSH administration is initiated on stimulation day one, and on average adequate follicular development is achieved by the ninth

day of treatment (range 6-18 days). Human chorionic gonadotrophin (hCG) can then be administered to induce final oocyte maturation.

A single injection of corifollitropin alfa would replace the first seven days of conventional rFSH (follitropin alfa or beta) in patients undergoing a gonadotrophin releasing hormone (GnRH) antagonist treatment protocol for controlled ovarian stimulation for assisted reproductive techniques (ART).

6. Comparator

The submission nominated conventional rFSH, (follitropin beta in particular) as the comparator. The PBAC considered that as previously, rFSH was the appropriate comparator.

7. Clinical Trials

The two key trials (ENGAGE and PURSUE) presented in the submission are described below:

ENGAGE: a direct randomised controlled trial (RCT) in women >60kg-90kg body weight and aged ≤36 years, comparing a single injection of corifollitropin alfa 150µg with daily injections of follitropin beta 200IU for the first seven days of stimulation, followed by daily injections of up to 200IU follitropin beta from stimulation day 8 in both arms.

The ENGAGE trial was the main basis for the PBAC recommendation of the listing of corifollitropin alfa 150µg for controlled ovarian stimulation in women undergoing ART procedures and weighing >60kg – 90kg.

PURSUE: a recently completed RCT in women ≥50kg body weight and aged between 35 years and 42 years, comparing a single injection of corifollitropin alfa 150µg with daily injections of follitropin beta 300IU for the first seven days of stimulation, followed by daily injections of up to 300IU follitropin beta from stimulation day 8 in both arms.

Publication details for PURSUE and previously unreported publication details for ENGAGE are presented in the table below.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
PURSUE Boostanfar R et al	A large double-blind efficacy and safety trial of corifollitropin alfa versus daily recombinant FSH in women 35 to 42 years of age undergoing ovarian stimulation prior to IVF or ICSI (PURSUE trial).	ASRM 68th Annual Meeting, San Diego, the USA, 20th – 24th October, 2012 (Abstract O-109)
ENGAGE Boostanfar et al	International differences in IVF live birth rates and cumulative ongoing pregnancy rates following ovarian stimulation with corifollitropin alfa or recombinant FSH.	*Fertility and Sterility* 2011; 96(3):S174.

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Boostanfar et al	A comparison of live birth rates and cumulative ongoing pregnancy rates between Europe and North America after ovarian stimulation with corifollitropin alfa or recombinant follicle-stimulating hormone.	*Fertility and Sterility* 2012; 97(6): 1351-8
Doody et al	No association between endogenous LH and pregnancy in a GnRH antagonist protocol: part I, corifollitropin alfa.	*Reproductive Biomedicine Online 2011; 23(4): 449-56*
Fatemi et al	A comparative evaluation of elevated progesterone during the late follicular phase of patients treated with corifollitropin alfa or daily RFSH.	*Human Reproduction 2012; 27 (Suppl 2): ii302-37. ESHRE 28th Annual Meeting, Istanbul, Turkey, 1 - 4 July, 2012 (Abstract P-566)*
Fatemi et al	High ovarian response does not jeopardize ongoing pregnancy rates and increases cumulative pregnancy rates in a GnRH-antagonist protocola.	*Human Reproduction 2012 November 7th [Epub ahead of print]*
Fauser et al	Pharmacokinetics and follicular dynamics of corifollitropin alfa versus recombinant FSH during ovarian stimulation for IVF.	*Reproductive Biomedicine Online* 2011; 22 (Suppl 1): S23-31
Hillensjo et al	Does treatment flexibility affect clinical outcome of either corifollitropin alfa or daily rFSH regimens?	*Human Reproduction* 2011; 26: i303-4.
Leader et al	Reduction of daily rFSH dose from stimulation day 8 onward in a corifollitropin alfa or rFSH treatment regimen does not compromise clinical outcome.	*Human Reproduction* 2011; 26: i302.
Mardesic et al	Success rates of early responders to corifollitropin alfa or daily rFSH in a large, randomized, double-blind trial.	*Human Reproduction* 2011; 26: i304.
Yding et al	P-560 A comparative evaluation of elevated progesterone at the start of stimulation in patients treated with corifollitropin alfa or daily rFSH.	*Human Reproduction* 2012; 27 (Suppl 2): ii302-37.

8. Results of Trials

The primary outcome in the submission was ongoing pregnancy rate (defined as the percentage of women with at least one foetus with heart activity ≥ 10 weeks after embryo transfer). In the PURSUE trial, vital pregnancy rate, i.e. the proportion of subjects with at least one foetus with heart activity ≥ 5 weeks after embryo transfer, was selected as the primary endpoint.

The PBAC had previously accepted ongoing pregnancy rate as a primary outcome for assessment of the treatment effect of corifollitropin alfa and Menopur® (hMG) in women participating in an ART program.

For assessment of the non-inferiority of corifollitropin alfa over follitropin beta, a predefined threshold of -8% was set for the lower bound of the two-sided 95% confidence interval (CI) of the difference in ongoing pregnancy rates between the two treatment groups.

In PURSUE, non-inferiority of corifollitropin alfa 150 micrograms to follitropin beta 300IU, in terms of the primary outcome of ongoing pregnancy rates, was demonstrated in both per attempt and per stage analyses in all intention-to-treat (ITT) patients, using a non-inferiority threshold of -8%. The PBAC noted the information presented in the hearing regarding minimally important clinical difference. The PBAC considered a difference of ±4% not ±8% as presented in the submission was reasonable in considering this data.

The PBAC recalled it had previously accepted the non-inferiority claim of corifollitropin alfa 150 micrograms relative to follitropin beta 200 IU in patients > 60kg, when the nominated non-inferiority margin was -8% as defined in the ENGAGE trial. However, in ENGAGE, the lower bounds of the 95% CIs of the risk differences (RDs) in ongoing pregnancy rates were much smaller than the specified non-inferiority margin, being -0.2% to -3.9% across all analysis datasets, and therefore non-inferiority would have been achieved even if the non-inferiority margin was much smaller. The PBAC recalled its November 2010 consideration that the predefined non-inferiority margin of -8% appeared large in terms of a patient relevant difference in pregnancy rates.

Across all datasets in the analysis, patients receiving 150 micrograms corifollitropin alfa had lower ongoing pregnancy rates than those treated with 300 IU conventional rFSH. Non-inferiority was demonstrated in all ITT analyses using a non-inferiority margin of -8%.

Results of ongoing pregnancy rates in all patients and in the subgroup of subjects >60kg body weight in PURSUE are summarised in the table below. Results from PURSUE, like those from ENGAGE, were presented according to "per stage" and "per attempt".

Results of ongoing pregnancy rates in the PURSUE trial

		Corifollitropin alfa 150µg n/N (%)	Follitropin beta 300IU n/N (%)	Risk difference % [95% CI][a]
All patients				
ITT analyses	Per attempt[b]	154/694 (22.2)	167/696 (24.0)	-1.9 [-6.1, 2.3][d]
	Per embryo transfer[c]	154/632 (24.4)	167/647 (25.8)	-1.6 [-6.2, 2.9][d]
Subgroup of patients >60kg				
ITT analyses	Per attempt[b]	113/510 (22.2)	121/477 (25.4)	-2.9 [-8.0, 2.2]
	Per embryo transfer[c]	113/470 (24.0)	121/446 (27.1)	-3.1 [-8.7, 2.6]
PP analyses	Per attempt[b]	104/459 (22.7)	107/440 (24.3)	-1.7 [-7.2, 3.9]
	Per embryo transfer[c]	104/420 (24.8)	107/409 (26.2)	-1.4 [-7.3, 4.5]

CI = confidence interval; ITT = intention-to-treat; PP = per protocol

[a] Corifollitropin alfa minus follitropin beta; from binomial regression model with identity link and factors for treatment and age class (≤38 yrs *vs* >38 yrs, as stratified)

[b] If a subject did not reach a certain stage in IVF treatment, zero values were imputed (eg if the particular subject did not have oocyte retrieval, then the number of oocytes, number of embryos etc. was set to zero and the pregnancy outcome was set to not pregnant)

[c] 'Per stage' analyses were restricted to subjects who reached a specific IVF stage, in this case only women who had embryo transfer.

[d] Data on risk differences and CIs in all-treated patients were retrieved from the clinical study report, as they are not presented in the submission.

From the subgroup of patients with >60 kg body weight, the non-inferiority margin was met in the PP-subgroup population, but not in the ITT-subgroup population. Although the subgroup analyses were underpowered, there was a clear trend that the lower bounds of risk

differences in ongoing pregnancy rates (-7.2% to -8.7%), indicating inferiority, are likely to be meaningful to women undergoing IVF/GIFT.

The PBAC noted that the dose of follitropin beta used in PURSUE was higher than that in ENGAGE (300IU *vs* 200IU) because the PURSUE trial involved women with increasing age (35 – 42 years) who have a reduced ovarian response and required a higher dose of FSH for ovarian stimulation. The use of a higher dose of follitropin beta in the comparator arm in the PURSUE trial was considered acceptable.

The PBAC noted the Economic Sub-Committee advice that body mass index rather than weight is associated with adverse pregnancy rates. In the PURSUE trial the large doses of rFSH reflected the older patient group. The PBAC noted results in the >90kg group were not provided as the group was very small (n=29). Rather, the submission relied on the total body of evidence.

The PBAC considered that the comparison of the results of the PURSUE study was difficult in the context of the wide range of rFSH doses used in these patients.

An overview of adverse events (AEs) in the PURSUE trial indicated that similar adverse events were reported in all-treated patients and in the subgroup of patients > 60 kg. Rates of all AEs, drug-related AEs and AEs leading to discontinuation were largely comparable between treatment groups. The difference in the rates of drug-related serious adverse events between the two treatment groups was 0% in the corifollitropin alfa arm vs 0.6% in the conventional rFSH arm.

The PBAC recalled its safety concerns regarding the incidence of ovarian hyperstimulation syndrome (OHSS) associated with use of corifollitropin when making its recommendation to list in 2011. From the results of the PURSUE trial, the PBAC noted the overall incidence of OHSS (mild, moderate, severe and unknown) was similar between the treatment arms (both 1.7%). In terms of severe OHSS, the PBAC noted there was a statistically significant difference between the treatment arms (0.9% follitropin beta versus 0.0% corifollitropin alfa, $p<0.05$).

The results of the pooled analysis of OHSS outcomes from the ENGAGE and PURSUE trials, presented by the sponsor are presented in the table below.

Pooled analysis of OHSS outcomes from ENGAGE and PURSUE

	Corifollitropin alfa 150 µg	**Follitropin beta 200-300 IU**
N	**1263**	**1230**
OHSS outcome	**n (%)**	**n (%)**
Severe	14 (1.1%)	16 (1.3%)

Total	62 (4.9%)	57 (4.6%)

Overall, the PBAC was reassured by the evidence presented that the use of corifollitropin in heavier females did not increase the rate of OHSS. The PBAC noted that combined OHSS data from clinical studies investigating corifollitropin alfa 150 micrograms (including PURSUE, ENGAGE and TRUST) and the latest Periodic Safety Update Report (PSUR) did not provide any additional information to alter interpretation of the known safety profile of corifollitropin alfa.

9. Clinical Claim

The submission claimed that corifollitropin alfa 150µg is non-inferior in terms of effectiveness and non-inferior in terms of safety compared to follitropin beta 200IU in women aged 18 to 36 years. The PBAC recalled it accepted that corifollitropin alfa (150µg) was non-inferior to follitropin beta (200IU) when restricting the PBS patient population to those most likely to respond to corifollitropin alfa and least likely to experience OHSS, based on the evidence from ENGAGE.

The submission claimed that corifollitropin alfa 150µg is non-inferior in terms of effectiveness and superior in terms of safety compared to follitropin beta 300IU in older women aged 35 to 42 years.
The PBAC considered that the effectiveness and safety claims for older women were not adequately supported by the evidence from the PURSUE trial.

10. Economic Analysis

The submission requested a review of the therapeutic relativity and price of corifollitropin alfa 150 micrograms compared to conventional rFSH, based on the new evidence provided by the PURSUE trial, regarding the comparative effectiveness of the two drugs in older women.

A cost-minimisation based on a non-inferiority claim for the effectiveness outcome of ongoing pregnancy rates, non-inferiority in terms of comparative safety in women aged 18 to 36, and superior comparative safety in women aged 35 to 42 (based on the rate of severe OHSS) was presented in the submission.

The equi-effective doses presented in the submission were:

- In younger women (≤ 34 years), corifollitropin alfa 150 micrograms as a single dose over 7 days and follitropin beta 200 IU as daily doses over 7 days (based on the ENGAGE trial); and
- In older women (≥ 35 years), corifollitropin alfa 150micrograms as a single dose over 7 days and follitropin beta 300 IU as daily doses over 7 days (based on the PURSUE trial).

On grounds of the uncertainty in a claim of non-inferiority in the PURSUE trial, the PBAC considered that there was no basis for changing the equi-effective dose previously agreed; corifollitropin alfa 150 micrograms as a single dose over seven days and follitropin beta 200 IU as daily doses over seven days for patients weighing greater than 60 kg.

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 over the first 5 years, at an estimated net cost per year to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC rejected the submission's request for a revised therapeutic relativity between corifollitropin and follitropin beta. The PBAC was not able to assess any specific data on patients whose weight was >90 kg owing to the small amount of data in the PURSUE trial. The PBAC considered the claim of non-inferiority between corifollitropin alfa and rFSH in the PURSUE trial may be doubtful, however the PBAC considered that it was reasonable to consider the products are non-inferior over the full range of patient weights. The PBAC noted that the doses of follitropin beta required are highly variable, patients are carefully selected for treatment on a range of factors including weight and age.

In considering the adverse event of OHSS the PBAC noted that the data from the PURSUE trial supported the view that there was no substantial difference in the incidence of OHSS in heavier patients. At the same time the PBAC noted that the trial population included only a small number of patients weighing > 90 kg. The PBAC was of the view that the previously applied cost offset for OHSS should be removed from the price of corifollitropin alfa.

In addition, the PBAC recommended that the weight limitation for subsidised treatment could be removed from the current restriction.

The PBAC noted that the submission meets the criteria for an Independent Review.

Recommendation

No changes were recommended for the 100 micrograms/0.5 mL presentation.

The PBAC recommended amending the current listing for corifollitropin alfa 150 micrograms/0.5 mL injection as follows.

Section 100 (IVF/GIFT Treatment)

Condition/Indication:	Controlled ovarian stimulation
Restriction:	Criteria for availability
Treatment criteria:	Patient must be receiving treatment as described in items 13200, 13201 or 13202 of the Health Insurance (General Medical Services Table) Regulations. AND Patient must be undergoing a gonadotrophin releasing hormone antagonist cycle.
Clinical criteria:	Patient must have an antral follicle count of 20 or less.

Administrative Advice	Supply of these items is through an accredited IVF/GIFT clinic. For enquiries relating to the IVF/GIFT Program, medical practitioners should contact the Department of Human Services on 1800 700 270.

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

MSD is pleased with the PBAC's recommendation to extend the listing for corifollitropin alfa to include women weighing more than 90 kg. On the other hand, MSD is disappointed with the PBAC's decision relating to the request for a revised therapeutic relativity between corifollitropin alfa and follitropin beta, but remains committed to working with the PBAC to resolve any uncertainties.