

## 5.07 FOLLITROPIN DELTA, solution for injection 12, 36, 72 micrograms, Rekovel® , Ferring Pharmaceuticals Pty Ltd

### 1 Purpose of application

- 1.1 Section 100 IVF Program Authority Required listing for follitropin delta for controlled ovarian stimulation (COS) in patients undergoing assisted reproductive technologies (ART).
- 1.2 The requested basis for listing was a cost-minimisation analysis versus follitropin alfa.
- 1.3 This is the first consideration of follitropin delta by the PBAC.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Women undergoing treatment with assisted reproductive technologies (ART), requiring controlled ovarian stimulation (COS)
Intervention	Follitropin delta, gonadotropin used for controlled ovarian stimulation (COS) as part of an ART cycle
Comparator	Follitropin alfa (Gonal F), gonadotropin used for COS as part of an ART cycle. This is not the only relevant comparator, but considered to be reasonable.
Outcomes	Ongoing pregnancy rate Ongoing implantation rate Live birth rate Oocyte count Appropriate ovarian response Cycle cancellation due to poor or excessive ovarian response
Clinical claim	Follitropin delta is no worse than follitropin alfa in terms of comparative clinical efficacy and safety. The claim regarding comparative efficacy requires consideration.

## 2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	No. of repeats	Dispensed price for maximum quantity Published [Effective]	Proprietary name and manufacturer
Follitropin delta 12 mcg/0.36 mL injection, 1 x 3 mL cartridge and 3 needles	5	0	\$ [REDACTED] [REDACTED]	Rekvelle Ferring Pharmaceutical
36 mcg/1.08 mL injection, 1 x 3 mL cartridge and 6 needles	5	0	\$ [REDACTED] [REDACTED]	
72 mcg/2.16 mL injection, 1 x 3 mL cartridge and 9 needles	4	0	\$ [REDACTED] [REDACTED]	

S100 IVF Program – Authority Required (Streamlined)  
5027  
Assisted Reproductive Technology  
Clinical criteria:  
Patient must be receiving medical services as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule

[\$ SPA] = price related to proposed special price arrangement

## 3 Background

### Registration status

- 3.1 Follitropin delta was approved by the TGA on 31 March 2017 for the following indication: “Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle”.
- 3.2 Follitropin delta is approved as a solution for injection in a cartridge administered with a re-usable multi-dose pen. The submission stated that an application has been submitted for administration via a disposable multi-dose pen. The submission is not requesting listing of the multi-dose pen.

## 4 Population and disease

- 4.1 In 2014, 33750 women had ART treatment in Australia and 13 had treatment in both Australia and New Zealand (Australia New Zealand Assisted Reproduction Database [ANZARD] 2016). ANZARD (2016) reports (p17) that 19.7% reported male infertility factors as the only cause of infertility; 30.8% reported only female infertility factors; 12.5% reported combined male-female factors; 22.3% reported unexplained infertility; and 14.7% were not stated. ANZARD (2016) also states that “However, the diagnostic definitions may vary among fertility centres and should be interpreted with caution”. The most recent national estimates indicate that 4.4% of all women who gave birth in Australia in 2013 received some form of ART treatment (ANZARD 2016).

## 5 Comparator

- 5.1 Follitropin alfa (Gonal F). This is the appropriate comparator.

- 5.2 Although a follitropin alfa biosimilar (Bemfola), follitropin beta (Puregon), corifollitropin (Elonva) and human menopausal gonadotropin (hMG; Menopur) are also listed on the PBS, and could represent additional relevant comparators, each have been listed on a cost-minimisation basis. The ex-manufacturer price per international unit (I.U.) for the follitropin alfa presentations is approximately \$0.36, and approximately \$0.46/I.U. for follitropin beta and human menopausal gonadotropin.

*For more detail on PBAC's view, see section 7 PBAC Outcome.*

## **6 Consideration of the evidence**

### **Sponsor hearing**

- 6.1 There was no hearing for this item.

### **Consumer comments**

- 6.2 PBAC noted and welcomed the input from health care professionals (3) and organisations (1) via the Consumer Comments facility on the PBS website. Input indicated that follitropin delta has a unique dose finding algorithm, and because it can deliver an individualised dose to patients it may minimise wastage and potentially lower costs to patients and the PBS. ACCESS Australia also expressed the view that follitropin delta could reduce the risk of Ovarian Hyperstimulation Syndrome, compared with other gonadotropins.

### **Clinical trials**

- 6.3 The submission is based on:
- one head-to-head randomised non-inferiority trial (ESTHER-1; n=1,329) comparing follitropin delta to follitropin alfa (Gonal F) in COS Cycle 1; and
  - one supplementary non-randomised, safety trial (ESTHER-2) comparing follitropin delta and follitropin alfa (Gonal F) that enrolled patients who did not achieve an ongoing pregnancy in ESTHER-1; patients maintained the treatment they were allocated to in ESTHER-1.
- 6.4 Details of the trials presented in the submission are provided Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trial		
ESTHER-1	Clinical Trial Report: A randomised, controlled, assessor-blind, parallel group, multicentre, multinational trial comparing the efficacy and safety of FE 999049 with follitropin alfa (GONAL-F) in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme. ESTHER-1 (Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World) Trial 000004.  Andersen A et al. Individualised versus conventional ovarian stimulation for in vitro fertilisation: a multicentre, randomised, controlled, assessor-blinded, phase 3 non-inferiority trial.	31 August 2015  Fertility and Sterility. 2016; 107 (2) 388-396
Supplementary non-randomised trial		
ESTHER-2	Clinical Trial Report: A controlled, assessor-blind, parallel group, multicentre, multinational trial evaluating the immunogenicity of FE999049 in repeated cycles of controlled ovarian stimulation in women undergoing an assisted reproductive technology programme. ESTHER-2 (Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World) Trial 000071.  Rasmussen B et al. Low immunogenicity potential of follitropin delta, a recombinant FSH preparation produced from a human cell line: Results from phase 3 trials (ESTHER-1 and ESTHER-2).	31 August 2015  Human Reproduction. 2016. 31 Suppl 1, i376 ABSTRACT No: P-574

Source: Table 2.2.3-1, p26 of the submission

6.5 The key features of the direct trials are summarised in Table 3. All trials included follow-up to live birth and neonatal health 4 weeks after birth.

**Table 3: Key features of the included evidence, follitropin delta versus follitropin alfa**

Trial	N	Design	Risk of bias	Patient population	Outcomes <sup>a</sup>	Use in economic evaluation
ESTHER-1 COS 1	1,329	R, SB, MC	Low	Women aged 18-40 years inclusive who were undergoing their first controlled ovarian stimulation cycle for IVF/ICSI.	Ongoing pregnancy rate Ongoing implantation rate	Used
ESTHER-2 COS 2 COS 3	513 188	SB, MC	Moderate	Patients failing to an ongoing pregnancy in ESTHER-1	Safety	Not used

COS=controlled ovarian stimulation cycle; MC=multi-centre; R=randomised, SB=single blind (assessor)

<sup>a</sup> primary

Source: compiled during the evaluation

6.6 Although both trials were only assessor-blinded, given the objective nature of the outcomes (ongoing pregnancy and implantation rate), this was not considered to introduce bias. The ESTHER-2 trial was considered to be at a moderate risk of bias given patients were not randomised (but maintained treatment they were allocated to in ESTHER-1) and lack of patient-blinding may have affected reporting of adverse events.

## Comparative effectiveness

6.7 Table 4 reports the co-primary outcomes of the ESTHER-1 trial, ongoing pregnancy and ongoing implantation rates. The results reported for the co-primary outcomes of ongoing pregnancy and ongoing implantation rates met the pre-defined non-inferiority margin of the ESTHER-1 trial of -8.0% in both the PP and mITT populations. In its consideration of corifollitropin, '[t]he PBAC considered a difference of  $\pm 4\%$ , not  $\pm 8\%$  as presented in the submission was reasonable in considering this data' for the outcome of ongoing pregnancy rates (Corifollitropin PSD, March 2013). Non-inferiority for follitropin delta was not met when applying a -4.0% margin to the ongoing pregnancy rate.

6.8 The Pre-Sub Committee Response (PSCR) (p1) reiterated that the non-inferiority margin of -8% for its two co-primary endpoints was pre-specified and agreed with the European Medicines Agency, and was based on regulatory precedence with corifollitropin. The PSCR also noted (Table 1, Attachment 1, p1) that wider limits than 4% have been used in the past for progesterone and other similar products

**Table 4: Results of the co-primary outcomes (ongoing pregnancy and implantation rate) reported in the ESTHER- 1 trial**

Analysis	Follitropin delta; n/N (%)	Follitropin alfa; n/N (%)	Relative risk (95% CI) <sup>d</sup>	Risk difference (95% CI)
Primary: Ongoing pregnancy - at least one intrauterine viable foetus				
PP <sup>a</sup>	198/623 (31.8)	206/632 (32.6)	0.98 (0.83, 1.14)	-0.9% (-6.0%, 4.3%)
mITT <sup>b</sup>	204/665 (30.7)	209/661 (31.6)	0.97 (0.83, 1.14)	-0.9% (-5.9%, 4.1%)
ITT <sup>c</sup>	204/666 (30.6)	209/663 (31.5)	0.97 (0.83, 1.14)	-0.9% (-5.9%, 4.1%)
Primary: Ongoing implantation – number of intrauterine viable foetuses 10-11 weeks after transfer divided by number of blastocysts transferred				
PP <sup>a</sup>	200/553 (36.2)	206/558 (36.9)	0.98 (0.84, 1.14)	-0.9% (-6.5%, 4.7%)
mITT <sup>b</sup>	206/585 (35.2)	209/584 (35.8)	0.98 (0.84, 1.15)	-0.6% (-6.1%, 4.8%)

Source: Table 2.5.1-1, p51; and Table 2.5.1-2, p51 of the submission

<sup>a</sup> exposed to randomised treatment and had no major protocol violations

<sup>b</sup> exposed to randomised treatment

<sup>c</sup> all randomised patients

<sup>d</sup> estimated using StatsDirect during the evaluation

CI = confidence interval; n = number of participants with event; N = total participants in group

6.9 Table 5 presents the secondary outcomes of the ESTHER-2 trial, ongoing pregnancy and ongoing implantation rates. No statistically significant differences were observed in ongoing pregnancy and implantation rates among women treated with follitropin delta and follitropin alfa. The rates observed in COS cycles 2 and 3 were comparable to those reported in COS cycle 1 (ESTHER-1). However ESTHER-2 was a safety trial and not powered to assess differences in these outcomes.

**Table 5: Results of the secondary outcomes (ongoing pregnancy and implantation rate) reported in the ESTHER-2 trial**

Cycle	Follitropin delta; n/N (%)	Follitropin alfa; n/N (%)	Relative risk (95% CI) <sup>a</sup>	Risk difference (95% CI) <sup>a</sup>
Ongoing pregnancy - at least one intrauterine viable foetus				
COS 2	70/252 (27.8)	67/261 (25.7)	1.08 (0.81, 1.44)	2.1% (-5.6%, 9.8%)
COS 3	26/95 (27.4)	26/93 (28.0)	0.98 (0.62, 1.55)	-0.6% (-13.4%, 12.2%)
Ongoing implantation – number of intrauterine viable foetuses 10-11 weeks after transfer divided by number of blastocysts transferred				
COS 2	73/254 (28.7)	69/271 (25.5)	1.13 (0.85, 1.49)	3.3% (-4.3%, 10.9%)
COS 3	33/132 (25.0)	35/121 (28.9)	0.86 (0.58, 1.30)	-3.9% (-3.4%, 5.7%)

Source: Table 2.5.1-5, p53 of the submission

Based on mITT population

<sup>a</sup> estimated using StatsDirect during the evaluation

6.10 Table 6 summarises the live birth rates in the ESTHER-1 and ESTHER-2 trials. No statistically significant differences were observed in live birth rates among women treated with follitropin delta and follitropin alfa. Neither ESTHER-1 nor ESTHER-2 were designed or powered to detect differences in the live birth rate, nor was a non-inferiority margin specified. The PBAC has previously accepted a -10% margin for live birth rates (Progesterone PSD, March 2014). Non-inferiority of follitropin delta compared with follitropin alfa was satisfied according to this criterion in COS Cycles 1 and 2, but not Cycle 3.

**Table 6: Live birth rates reported in the ESTHER-1 and ESTHER-2 trials**

	Follitropin delta; n/N (%)	Follitropin alfa; n/N (%)	Relative risk (95% CI) <sup>a</sup>	Risk difference (95% CI)
ESTHER-1 (COS 1)				
PP	192/623 (30.8)	200/632 (31.6)	0.97 (0.83, 1.15)	-0.9% (-6.0%, 4.2%)
mITT	198/665 (29.8)	203/661 (30.7)	0.97 (0.82, 1.14)	-0.9% (-5.8%, 4.0%)
ESTHER-2				
COS 2 (mITT)	69/252 (27.4)	66/261 (25.3)	1.08 (0.81, 1.45)	2.3% (-5.3%, 9.9%)
COS 3 (mITT)	25/95 (26.3)	25/93 (26.9)	0.98 (0.61, 1.57)	0.0% (-12.6%, 12.7%)

Source: Table 2.5.1-7, p54 of the submission

## Comparative harms

6.11 No statistically significant differences were observed between follitropin delta and follitropin alfa in terms of adverse events, adverse events leading to death (one in both arms), serious adverse events, adverse events leading to discontinuation, severe adverse events or adverse drug reactions.

6.12 Ovarian hyperstimulation syndrome (OHSS) is a particular adverse event that may occur during controlled ovarian stimulation. There was no statistically significant difference in the rate of early OHSS events reported in women treated with follitropin delta and follitropin alfa in ESTHER-1, however statistically fewer women treated with follitropin delta experienced (i) any preventative intervention for OHSS, (ii) early OHSS (any grade) and/or preventative intervention and (iii) early OHSS (moderate/severe) and/or preventative intervention. No differences were observed in the incidence of

late OHSS between the treatment groups in ESTHER-1. In total during ESTHER-2, OHSS (early and late) and/or preventive interventions for early OHSS occurred in 2.3% of follitropin delta cycles and 3.7% of follitropin alfa cycles.

### Interpretation of clinical evidence

6.13 The submission claimed that follitropin delta, in an individualised fixed daily dosage protocol (based on AMH and body weight), is non-inferior in terms of effectiveness and safety compared with follitropin alfa (with dose adjustment during treatment) in the clinical trial setting and in the Australian clinical setting. The ESC considered that on the basis that the non-inferiority margin was pre-defined and given the previous PBAC considerations in this area, the claim of non-inferiority was reasonable.

6.14 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.15 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

### Economic analysis

6.16 Table 7 presents the key assumptions and components of the cost-minimisation approach presented by the submission.

**Table 7: Key assumptions and components of the cost-minimisation approach**

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2 of the submission, effectiveness is assumed to be non-inferior. This requires consideration as although non-inferiority was established based on the non-inferiority margin prespecified in the ESTHER-1 trial (-8.0%), non-inferiority was not established based on a non-inferiority margin previously accepted by the PBAC (-4.0%) for the outcome of ongoing pregnancy.
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is reasonably assumed to be non-inferior.
Evidence base	Direct randomised trials
Equi-effective doses	ESTHER-1: Mean (SD) 90.0 mcg (25.3) follitropin delta $\equiv$ 1,414 IU (458.6) follitropin alfa Base case: Mean [REDACTED] follitropin delta $\equiv$ [REDACTED] follitropin alfa
Direct medicine costs	Drug cost, equivalent cost per cycle
Other costs or cost offsets	No

Source: Table 3B.1.1, p80 of the submission

6.17 The equi-effective doses were reported to be: 90.0 mcg follitropin delta to 1,414 IU follitropin alfa in the ESTHER-1 trial.

6.18 The submission presents a cost-minimisation analysis based on a relativity of: [REDACTED] follitropin delta to [REDACTED] follitropin alfa.

6.19 The justification provided in the submission for use of this alternative relativity is that:

- there were notable differences in the baseline characteristics of women enrolled in the ESTHER-1 trial and the likely PBS population, which would result in differing doses of follitropin delta in the Australian compared with ESTHER-1 population; and
  - although dosing of follitropin alfa in the ESTHER-1 trial (all women were initiated on 150 IU per day) was consistent with the TGA-approved PI, the submission states there is variation in starting dose (recommended to be 150 IU to 225 IU in the PI) and in dose adjustments during the cycle in the Australian setting compared with those observed in ESTHER-1.
- 6.20 For subsequent treatment cycles, the daily dose of follitropin delta should be maintained or modified according to the patient's ovarian response in the previous cycle. Doses of follitropin delta remain fixed within a given stimulation cycle. This is in contrast to the currently PBS-listed gonadotropins where the dose may be adjusted during a stimulation cycle, according to response.
- 6.21 As a result of these differences, the submission presents an analysis in Appendix 2.4 to the submission, where the mean doses are estimated based on the mean total follicle stimulating hormone (FSH) dose per cycle for follitropin alfa used in a cohort of first cycle patients in an Australian clinical setting [REDACTED] and the predicted dose of follitropin delta in the same cohort (based on individual patient AMH and body weight). Although the submission provides sufficient information to establish that the patients included in the cohort investigated are representative of the larger IVF population, the submission has not provided any evidence that the dose of follitropin alfa in this particular clinical setting is representative of follitropin alfa dosing nationally. It may be expected that IVF clinics have protocols in place and these may differ from clinic to clinic.
- 6.22 The PSCR (p2) claimed that the clinic used for this calculation is a large Australian clinic that is part of a larger IVF group which regularly reviews its practices and outcomes across its clinics. Further, the PSCR argued that prescribing data for the local clinic appears consistent with national dispensing data, suggesting the local clinic dosing is broadly representative of the Australian patient population. However, the ESC was of the view that although the data submitted is from a large clinic, it is possible that other IVF clinics have different protocols in place.
- 6.23 Although it is acknowledged that differences exist in both population characteristics and potentially in dosing of follitropin alfa, one major limitation of the use of the 'alternative' relativity is that there is no clinical outcome data (ongoing pregnancy or ongoing implantation rate) to substantiate the submission's claim that [REDACTED] follitropin delta is equivalent to [REDACTED] follitropin alfa.
- 6.24 Additionally, while differences in the populations were identified in terms of body weight, age, proportion undergoing 1, 2 or 3 COS cycles, cause of infertility and follitropin alfa dosing; the only factor explicitly adjusted in the cost-minimisation analysis was the assumed follitropin delta and follitropin alfa doses.

- 6.25 The ESC noted that the PSCR (p1-2) stated that the analysis presented in the PSCR suggested that higher FSH doses were associated with lower clinical pregnancy rates in the Australian patient population. The ESC considered that the higher doses could therefore not be linked back to comparable outcomes to the trial, and thus the ‘real world’ equi-effective doses had greater uncertainty.
- 6.26 On balance, the ESC agreed that the trial based equieffective doses should be used, but that it would be reasonable to adjust these doses for differences in weight and age in the Australian population compared to the trial. This would result in an equi-effective dose on 1,896 IU follitropin alfa to 93.6 mcg follitropin delta.
- 6.27 The pre-PBAC response maintained that the best estimate of use in the Australian clinical setting was the AU-First-Cycle scenario which indicated an equi-effective dose of [REDACTED] follitropin alfa to [REDACTED] follitropin delta. However, the sponsor also acknowledged that there was uncertainty in the analysis of the AU-First-Cycle population compared to the AU-ESTHER-criteria population, and that the proposed doses would likely not be associated with any compromise in efficacy or safety. While the sponsor maintained that the proposed therapeutic relativity underestimates the value of follitropin delta, the pre-PBAC response indicated a willingness to accept the equi-effective dose of 1,896 IU follitropin alfa to 93.6 mcg follitropin delta proposed by the ESC.
- 6.28 The PBAC noted the sponsor’s proposal in the pre-PBAC response to adjust the equi-effective dose on the basis of a difference in the actual versus expected utilisation, or to use clinical data from a planned prospective trial of pregnancy outcomes with follitropin delta. The PBAC considered that such a request would need to be put forward and considered as part of a separate major submission to alter the basis of the existing recommendation, when the data became available.

**Drug cost/patient/course: \$ [REDACTED]**

- 6.29 The estimated cost per course of treatment with follitropin delta is \$ [REDACTED] based on the effective price (\$ [REDACTED] based on the published price), assuming the maximum daily dose allowed in COS cycle 1 of 12 mcg/day and 15 days of treatment. This may be an overestimate as the dose of follitropin delta in the first COS cycle is based on AMH levels and body weight (e.g. a woman weighing 60 kg with AMH  $\geq 40$  would require 0.10 mcg/kg or 6 mcg/day) and mean days of treatment in the ESTHER-1 trial was nine days.
- 6.30 This compares with \$1,684.55 per script of follitropin alfa (Gonal F) 900 IU and \$2,114.10 per script of follitropin beta (Puregon) 900 IU. The financial estimates in the submission assume one script of follitropin delta will replace one script of follitropin alfa or follitropin beta.
- 6.31 Doses of follitropin delta for subsequent COS cycles are difficult to determine as they are based on ovarian response in the previous cycle.

## Estimated PBS usage & financial implications

6.32 This submission was not considered by DUSC.

6.33 The submission reasonably estimates the financial impact of listing follitropin delta on the PBS using a market share approach.

6.34 Table 8 summarises the estimated financial implication of listing follitropin delta on the PBS.

**Table 8: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed	■	■	■	■	■	■
<b>Estimated financial implications of follitropin delta</b>						
Cost to PBS/RPBS less copayments (effective) <sup>a</sup>	■	■	■	■	■	■
Cost to PBS/RPBS less copayments (published) <sup>a</sup>	■	■	■	■	■	■
<b>Estimated financial implications for follitropin alfa and beta</b>						
Cost to PBS/RPBS less copayments <sup>b</sup>	■	■	■	■	■	■
<b>Net financial implications</b>						
Net cost to PBS/RPBS/MBS/DHS (effective)	■	■	■	■	■	■
Net cost to PBS/RPBS/MBS/DHS (published)	■	■	■	■	■	■

Source: Table 4.2.2-3, p87; Table 4.2.2-4, p88; Table 4.2.3-1, p88; Table 4.2.4-1a, p89; Table 4.2.4-1b, p90; Table 4.3.1, p91; Table 4.4-1a, p91 and Table 4.4-1b, p92 of the submission

<sup>a</sup> assuming 84% of patients are dispensed a single script of 36 mcg/1.08 mL and 16% are dispensed a single script of 72 mcg/2.16 mL follitropin delta

<sup>b</sup> assuming equal replacement of one script of follitropin alfa 900 I.U or follitropin beta 900 I.U per one script of follitropin delta

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to Government, based upon published prices, would be less than \$10 million per year.

6.35 The net savings estimated by the submission when applying follitropin delta effective prices is largely driven by the effective price being derived from a cost-minimisation analysis versus follitropin alfa, but assuming replacement of both follitropin alfa and follitropin beta in the financials, where follitropin beta has a higher DPMQ. It is unclear that assuming the same rate of substitution from follitropin alfa and beta is reasonable given that follitropin alfa has twice the market share of follitropin beta. Should the substitution of follitropin beta be less than assumed by the submission, this net saving will be an overestimate. The PSCR (p3) acknowledges that the estimated net savings are driven by replacement of follitropin beta with follitropin delta, and continued to assume equal probability of substitution since there is no established difference in efficacy or safety between the two gonadotropins. The PSCR also argued that the lower market share of follitropin beta could make its continuing

erosion more likely as it could reflect a lower propensity of prescribers to continue with prescribing this treatment.

- 6.36 The ESC agreed with the PSCR that the uptake rates for follitropin delta would not be influenced by the requirement for AMH testing because most patients will get this test as a standard part of commencing fertility treatments.
- 6.37 The ESC noted that the extent of savings will be dependent on the equi-effective doses, and the rate of substitution.
- 6.38 No risk sharing arrangements were proposed by the submission. However the PSCR (p 4) indicates the sponsor's willingness to negotiate such an arrangement.
- 6.39 The submission requested a Special Pricing Arrangement. Although not a matter for the PBAC, the committee noted that Special Pricing Arrangements are only available in limited circumstances in accordance with criteria agreed by Cabinet. In particular, Special Pricing Arrangements are only available for new drugs seeking listing on a cost-minimisation basis with a currently listed drug, if the currently listed drug already has a Special Pricing Arrangement; follitropin alpha does not have a Special Pricing Arrangement. The PSCR (p 4) argued that follitropin delta has unique characteristics compared to any available alternative therapies. Specifically, 'whilst other gonadotrophins including the comparator, follitropin alfa, are also indicated for controlled ovarian stimulation, follitropin delta doses are prospectively individualised and remain fixed throughout the cycle to achieve optimum response according to routinely measured patient characteristics including body weight and Anti-Müllerian hormone (AMH). This has been demonstrated to achieve a higher proportion of patients achieving the targeted number of oocytes and a reduction in the proportion of women requiring measures to prevent OHSS and/or experiencing OHSS'. However, the PBAC noted that the submission did not make a claim of superior safety compared to the currently listed products.

## Quality use of medicines

- 6.40 The submission proposed education for prescribers given the altered fixed-dose regimen for follitropin delta within a controlled ovarian stimulation cycle which differs from the currently PBS-listed gonadotropins where dose adjustments may be made during the stimulation period. The Sponsor has also developed an App to aid clinicians to identify the appropriate dose based on AMH levels and body weight.

*For more detail on PBAC's view, see section 7 PBAC Outcome.*

## 7 PBAC Outcome

- 7.1 The PBAC recommended the listing, under a S100 special arrangement of follitropin delta for controlled ovarian stimulation (COS) in patients undergoing assisted reproductive technologies (ART), on a cost-minimisation basis against follitropin alfa, with an equi-effective dose of 1,896 IU follitropin alfa to 93.6 mcg follitropin delta.

- 7.2 The PBAC accepted the nominated comparator, follitropin alfa, as it is the most commonly used form of follitropin on the PBS, and noted that the other follitropin products available on the PBS were all listed on a cost-minimisation basis to follitropin alfa and none of the other follitropin products have subsequently undergone price reductions.
- 7.3 The PBAC accepted the submission's claim of non-inferior effectiveness against follitropin alfa, on the basis that the pre-specified non-inferiority margin of  $\pm 8.0\%$  was achieved and was comparable to other previously accepted measures in this treatment setting.
- 7.4 The PBAC did not agree with the sponsor's estimate of the equi-effective dose of [REDACTED] follitropin alfa against [REDACTED] follitropin delta. The PBAC did not accept that the doses derived from the analysis of the population data were reasonable, particularly in the context of the additional evidence that suggests an inverse relationship between increasing dose and pregnancy outcomes. However, the Committee considered it was reasonable to adjust the equi-effective dose from the ESTHER-1 trial to account for the difference in weight and age between the clinical trial population and the Australian population. The PBAC therefore agreed with the ESC that the equi-effective dose should be 1,896 IU of follitropin alfa to 93.6 mcg of follitropin delta.
- 7.5 The PBAC also noted that any requests to change the basis of this cost-minimisation recommendation in the future would need to be in the form of a major submission.
- 7.6 The PBAC agreed that the requested listing was likely to result in a saving to the PBS, but that the extent of savings will be dependent on the rate of substitution between follitropin alfa and follitropin beta, and the estimates will need to be updated to account for the revised equi-effective dose.
- 7.7 The PBAC advised that follitropin delta is not suitable for prescribing by nurse practitioners.
- 7.8 The PBAC recommended that the Early Supply Rule should not apply.
- 7.9 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommend

## 8 Recommended listing

### 8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
FOLLITROPIN DELTA			Rekovele	Ferring Pharmaceutical
12 mcg/0.36 mL injection, 1 x 3 mL cartridge and 3 needles	5	0		
36 mcg/1.08 mL injection, 1 x 3 mL cartridge and 6 needles	5	0		
72 mcg/2.16 mL injection, 1 x 3 mL cartridge and 9 needles	4	0		

<b>Category / Program</b>	Section 100 – IVF
<b>Prescriber type:</b>	<input checked="" type="checkbox"/> Medical Practitioners
<b>PBS Indication:</b>	Assisted Reproductive Technology
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must be receiving medical services as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule

### 8.2 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
FOLLITROPIN DELTA			Rekovele	Ferring Pharmaceutical
12 mcg/0.36 mL injection, 0.36 mL injection device	5	0		
36 mcg/1.08 mL injection, 1.08 mL injection device	5	0		
72 mcg/2.16 mL injection, 2.16 mL injection device	4	0		

<b>Category / Program</b>	Section 100 – IVF
<b>Prescriber type:</b>	<input checked="" type="checkbox"/> Medical Practitioners
<b>PBS Indication:</b>	Assisted Reproductive Technology
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must be receiving medical services as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule

## 9 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.

## **10 Sponsor's Comment**

Ferring welcomes the PBAC decision to recommend the listing on the PBS of REKOVELLE, follitropin delta (rhu) and is pleased that Australian women undergoing assisted reproductive technologies will have access to controlled ovarian stimulation using an evidence-based individualised dosing regimen.