

5.15 FOLLITROPIN ALFA (biosimilar)

75 units (5.5 microgram)/0.125 mL injection, 5 x 0.125 mL injection devices

150 units (11 microgram)/0.25 mL injection, 5 x 0.25 mL injection devices

225 units (16.5 microgram)/0.375 mL injection, 5 x 0.375 mL injection devices

300 units (22 microgram)/0.5 mL injection, 5 x 0.5 mL injection devices

450 units (33 microgram)/0.75 mL injection, 5 x 0.75 mL injection devices

Bemfola®, FINOX Biotech Australia

1 Purpose of Application

1.1 The minor submission requested:

- A Section 100 (In-Vitro Fertilisation (IVF) Program) listing of Bemfola® (follitropin alfa) for treatment of women who are undergoing assisted reproductive technology (ART);
- A Section 85 listing of Bemfola® for treatment of women with anovulatory infertility and for men with infertility due to hypogonadotropic hypogonadism.

1.2 The Minister (delegate) also requested the PBAC provide advice under section 101(3) of the National Health Act 1953 (the Act) on the marking Bemfola as equivalent (i.e. “a” flagging) to Gonal-f® (follitropin alfa) in the Schedule.

1.3 The minor submission indicated that Bemfola is a similar biological medicinal product (SBMP) to the current PBS listed brand of Gonal-f. Gonal-f is listed on the PBS for the same clinical indications as requested for Bemfola.

2 Requested listing

2.1 The minor submission sought new listings in the General Schedule and Section 100 (IVF Program), as follows. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough:

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Name, Restriction, Manner of administration and form	Max. Qty Units	№.of Rpts	Dispensed Price for Max. Qty	Proprietary and Manufacturer	Name
FOLLITROPIN ALFA 75 units (5.5 microgram)/0.125 mL injection, 5 x 0.125 mL injection devices	15	0	\$ [REDACTED]	Bemfola®	FINOX Biotech Australia
150 units (11 microgram)/0.25 mL injection, 5 x 0.25 mL injection devices	15	0	\$ [REDACTED]		
225 units (16.5 microgram)/0.375 mL injection, 5 x 0.375 mL injection devices	15	0	\$ [REDACTED]		
300 units (22 microgram)/0.5 mL injection, 5 x 0.5 mL injection devices	15	0	\$ [REDACTED]		
450 units (33 microgram)/0.75 mL injection, 5 x 0.75 mL injection devices	15	0	\$ [REDACTED]		
Category / Program	Section 100 – IVF				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
Condition:	Controlled ovarian hyperstimulation <i>Assisted Reproductive Technology</i>				
PBS Indication:	Controlled ovarian hyperstimulation in women undergoing assisted reproductive technologies <i>Assisted Reproductive Technology</i>				
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined				
Clinical criteria:	Patient must be receiving medical services as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule				

Name, Restriction, Manner of administration and form	Max. Qty Units	№.of Rpts	Dispensed Price for Max. Qty	Proprietary and Manufacturer	Name
FOLLITROPIN ALFA 75 units (5.5 microgram)/0.125 mL injection, 5 x 0.125 mL injection devices	15	1	\$ [REDACTED]	Bemfola®	FINOX Biotech Australia
150 units (11 microgram)/0.25 mL injection, 5 x 0.25 mL injection devices	15	1	\$ [REDACTED]		
225 units (16.5 microgram)/0.375 mL injection, 5 x 0.375 mL injection devices	15	1	\$ [REDACTED]		
Category / Program	Section 85				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
Condition:	Anovulatory infertility Hypogonadotrophic hypogonadism				
PBS Indication:	<i>Anovulatory infertility</i> For the treatment of anovulatory infertility in women who have been unresponsive to clomiphene citrate or where clomiphene citrate is contraindicated				
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined				

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Administrative Advice	<p>NOTE: Except in cases of hypopituitarism or primary amenorrhoea, the patient should have been adequately treated with clomiphene citrate and/or gonadorelin and failed to have conceived. Women who have had apparent ovulation induced by other agents and have failed to conceive should have laparoscopic evidence that there is no other impediment to conception. Oligomenorrhoea should have been present for at least twelve months or amenorrhoea for at least six months prior to treatment. Patients with hyperprolactinaemia should have had appropriate surgical or medical treatment prior to treatment.</p>
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Condition:	<p>Anovulatory infertility Hypogonadotrophic hypogonadism Infertility</p>
PBS Indication:	<p>Bemfola is indicated with concomitant human chorionic gonadotrophin (hCG) therapy for the stimulation of spermatogenesis in gonadotrophin deficient men in whom hCG alone is ineffective Infertility</p>
Clinical criteria	<p>The condition must be due to hypogonadotrophic hypogonadism, AND The treatment must be following failure of 6 months' treatment with human chorionic gonadotrophin to achieve adequate spermatogenesis, AND The treatment must be administered with human chorionic gonadotrophin.</p>
Population criteria	<p>Patient must be male.</p>
Restriction Level / Method:	<p><input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined</p>
Administrative Advice	<p>NOTE: Except in cases of hypopituitarism or primary amenorrhoea, the patient should have been adequately treated with clomiphene citrate and/or gonadorelin and failed to have conceived. Women who have had apparent ovulation induced by other agents and have failed to conceive should have laparoscopic evidence that there is no other impediment to conception. Oligomenorrhoea should have been present for at least twelve months or amenorrhoea for at least six months prior to treatment. Patients with hyperprolactinaemia should have had appropriate surgical or medical treatment prior to treatment.</p>

2.2 To be eligible, women receiving Bemfola for controlled ovarian hyperstimulation as part of an ART service must be receiving the services described in items 13200, 13201, 13202 or 13203 of the MBS. The description of these MBS items and their fees are summarised in Table 1. Each dose of Bemfola is tailored to the individual patient according to response. Using the total dose reported in the key trial FIN3001, the cost of Bemfola was estimated to be \$ [REDACTED] per cycle per woman undergoing assisted reproduction (excluding any wastage, refer to the “Economic analysis” section for calculations).

Table 1: MBS items associated with the proposed Section 100 - IVF listing of Bemfola

Item	Description	MBS fee/benefit
13200	Assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval, involving the use of drugs to induce superovulation and including quantitative estimation of hormones, ultrasound examinations, all treatment counselling and embryology laboratory services but excluding artificial insemination, transfer of frozen embryos or donated embryos or ova or a service to which item 13201, 13202, 13203, 13206 or 13218 applies, being services rendered during 1 treatment cycle - initial cycle in a single calendar year	Fee: \$3,110.75 Benefit: 75% = \$2,333.10 85% = \$3,031.25
13201	Assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval, involving the use of drugs to induce superovulation and including quantitative estimation of hormones, ultrasound examinations, all treatment counselling and embryology laboratory services but excluding artificial insemination, transfer of frozen embryos or donated embryos or ova or a service to which item 13200, 13202, 13203, 13206 or 13218 applies, being services rendered during 1 treatment cycle - each cycle after the 1st in a single calendar year	Fee: \$2,909.75 Benefit: 75% = \$2,182.35 85% = \$2,830.25
13202	Assisted reproductive technologies superovulated treatment cycle that is cancelled before oocyte retrieval, involving the use of drugs to induce superovulation and including quantitative estimation of hormones and ultrasound examinations, but excluding artificial insemination, transfer of frozen embryos or donated embryos or ova or a service to which item 13200, 13201, 13203, 13206 or 13218 applies, being services rendered during 1 treatment cycle	Fee: \$465.55 Benefit: 75% = \$349.20 85% = \$395.75
13203	Ovulation monitoring services for artificial insemination, including quantitative estimation of hormones and ultrasound examinations, being services rendered during 1 treatment cycle but excluding a service to which item 13200, 13201, 13202, 13206, 13212, 13215 or 13218 applies	Fee: \$486.75 Benefit: 75% = \$365.10 85% = \$413.75

3 Background

3.1 Bemfola was approved for registration by the TGA as a biosimilar medicine for the following indications:

- For controlled ovarian hyperstimulation in women undergoing ART;
- For the treatment of anovulatory infertility in women who have been unresponsive to clomiphene citrate or where clomiphene citrate is contraindicated;
- In combination with a luteinising hormone (LH) preparation for the stimulation of follicular development in women with severe LH and follicle-stimulating hormone (FSH) deficiency^a; and
- With concomitant hCG therapy for the stimulation of spermatogenesis in gonadotrophin-deficient men in whom hCG alone is ineffective.

3.2 The minor submission did not request a PBS listing of Bemfola, in combination with LH, for women with severe LH and FSH deficiency, as the comparator (Gonal-f) is not PBS listed for this indication.

^a In clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/L.

- 3.3 Through the TGA biosimilar evaluation pathway, the TGA Delegate considered the evidence from Trials FIN1001 and FIN3001 (same trials presented in the minor PBAC submission) and concluded that “the study satisfactorily demonstrated bioequivalence and the clinical study satisfactorily demonstrated equivalence for the primary and most of the secondary endpoints in an appropriate and sensitive population” (p13, Delegate’s Overview). At a meeting in October 2015 of the Advisory Committee on Prescription Medicines (ACPM), the ACPM resolved to recommend to the TGA Delegate of the Minister and the Secretary that Bemfola has an overall positive benefit-risk profile for the proposed indications.
- 3.4 Bemfola is the first follitropin biosimilar registered in Australia and has not been previously considered by the PBAC.
- 3.5 At its December 1997 meeting, the PBAC recommended the listing of follitropin alfa (Gonal-f) on the PBS in the Section 100 IVF Program (for women undergoing ART) and as a Restricted Benefit listing in the General Schedule (for women with anovulatory infertility and for male infertility due to hypogonadotropic hypogonadism) on the basis of equivalency to follitropin beta.
- 3.6 A minor submission from the sponsor of Gonal-f (Merck Serono) is due to be considered at the PBAC meeting in March 2016, along with the Bemfola submission, with a request that Gonal-f should not be ‘a’-flagged to Bemfola or any further follitropin alfa biosimilar (refer to Other Matters, PBAC March 2016 Outcomes).

4 Clinical place for the proposed therapy

- 4.1 Bemfola is a recombinant human follicle stimulating hormone (r-hFSH) (follitropin alfa). FSH is a pituitary glycoprotein hormone which plays a key role in regulating reproductive function in both females and males. Once secreted into the blood stream by the endocrine cells of the anterior pituitary, FSH controls ovarian follicular growth in females and induces spermatogenesis in males. Deficiency of FSH leads to ovulatory failure or dysfunction in women and impaired spermatogenesis in men.
- 4.2 Bemfola is proposed to be used as an alternative to Gonal-f: 1) in women undergoing controlled ovarian stimulation for ART; 2) for treatment of women with anovulatory infertility; and 3) in combination with hCG, for stimulation of spermatogenesis in gonadotrophin-deficient men who have failed hCG therapy.

5 Comparator

- 5.1 The minor submission appropriately nominated Gonal-f as the main comparator. The main arguments provided in support of this nomination are: 1) both Bemfola and Gonal-f are r-hFSH (follitropin alfa); and 2) Gonal-f is currently available and listed on the PBS for the same indications as those proposed for Bemfola.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (3) and an organisation (1) via the Consumer Comments facility on the PBS website. Many of the comments expressed concern about potential substitution between the biosimilar and reference biologic. Correspondence from Access Australia highlighted that training of patients on how to administer medications is brand specific due to different delivery systems and that clinicians may wish to maintain a particular brand for some patients “if they have any concerns (real or perceived) of intra-patient variability of the products.”

Clinical trials

6.3 The minor submission presented two direct randomised trials:

- FIN1001: comparing the clinical pharmacokinetic and safety profiles of Bemfola with Gonal-f in healthy females (n=25);
- FIN3001: comparing the efficacy and safety of Bemfola with Gonal-f in women undergoing ART (n=410).

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

Trial ID	Protocol title/ Publication title	Publication citation
FIN1001	Clinical study report FIN1001. Comparative pharmacokinetics of AFOLIA and Gonal-f® after single subcutaneous application.	December 2009
	Wolzt M., Gouya G., Sator M., <i>et al.</i> Comparison of pharmacokinetic and safety profiles between Bemfola® and Gonal-f® after subcutaneous application.	<i>European Journal of Drug Metabolism and Pharmacokinetics</i> 2015 [Epub ahead of print]
FIN3001	Clinical study report FIN3001. A Phase III assessor-blinded randomised parallel group multi-centre study to compare efficacy and safety of two r-hFSH formulations (AFOLIA vs Gonal-f®) in women for assisted reproductive treatment.	September 2012
	Rettenbacher M., Andersen A.N., Garcia-Velasco J.A., <i>et al.</i> A multi-centre phase 3 study comparing efficacy and safety of Bemfola® versus Gonal-f® in women undergoing ovarian stimulation for IVF.	<i>Reproductive BioMedicine Online</i> 2015; 30(5): 504-13

Source: Table 2-1, pp12-13 of the minor submission

6.4 The minor submission indicated that the pharmacokinetic and clinical evidence concerning Bemfola was developed in line with the European Medicines Agency (EMA) guideline on non-clinical and clinical development of similar biological medicinal products containing r-hFSH.

6.5 The minor submission did not present clinical evidence on the use of Bemfola versus Gonal-f for the treatment of anovulatory infertility in women or for stimulation of spermatogenesis in gonadotrophin-deficient men. Both the US Food and Drug

Administration (FDA) and the EMA specify criteria for extrapolating findings concerning the efficacy and safety of the follow-on biological product in one clinical indication to other clinical indications of the reference biological product. These criteria include: i) whether there is the same clinically relevant mechanisms of action for the different clinical indications; and ii) whether the assessment has occurred in the most sensitive clinical condition, in order to detect clinically meaningful differences in efficacy and safety, particularly immunogenicity. In the current submission it would be reasonable to assume that ART is the most sensitive indication, as a small difference in the level of stimulation produced by follitropin alfa could have clinically relevant impacts on health outcomes in women with different causes of infertility and with individually variable responses to treatment. The other proposed PBS indications, namely anovulatory infertility and hypogonadotropic hypogonadism, are mediated through the same well-characterised receptor system as ART. Both the TGA and the EMA considered that the extrapolation of clinical findings in women receiving ART to anovulatory infertility and hypogonadotropic hypogonadism was scientifically justified.

- 6.6 The minor submission did not provide any evidence demonstrating the efficacy and safety of drug switching between Bemfola and Gonal-f either within or between treatment cycles in the proposed PBS populations.
- 6.7 The key features of the two trials presented in the minor submission are summarised in Table 3.

Table 3: Key features of Trials FIN1001 and FIN3001

Component	FIN1001	FIN3001
Study design	Randomised, open-label, two-period, cross-over, bioequivalence trial	Randomised, assessor-blinded, multi-centre, equivalence trial
Overall risk of bias	Low	Low
Number of patients randomised	N=25	N=410
Key eligibility criteria	<ul style="list-style-type: none"> – Healthy women; – Between 18-38 years; – Use of oral contraceptives for at least 3 months before study entry; and – Excluded if with presence of PCOS or with a history of hypersensitivity to FSH (OHSS). 	<ul style="list-style-type: none"> – Women aged between 20-38 years; – First or second cycle in the present series of ART; – Infertility due to tubal factor, mild endometriosis, male factor or unexplained infertility; – Basal FSH <10IU/L (cycle day 2-5); – E2 levels <50pg/mL (<0.18nmol/L) at the day of FSH administration; – AFC of 10-25 (sum of both ovaries); – Excluded if with PCOS or with presence/history of OHSS; and – Excluded if with a history of poor response to gonadotropin treatment^a
Treatment regimen of r-hFSH during the trial	Bemfola® 225IU single SC dose, followed by Gonal-f® 225IU single SC dose at an interval of 14 days. Or <i>vice versa</i> .	Bemfola® or Gonal-f® 150IU SC daily for a maximum of 16 days.
Concomitant medicines	Enantone®-Gyn (leuprorelin acetate) given prior to each injection of Bemfola® or Gonal-f® to down regulate endogenous FSH levels	<ul style="list-style-type: none"> – GnRH agonist during the screening phase, administered according to centre's procedures to all eligible patients in the luteal phase – Ovitrelle® (a hCG) for ovulation induction.

Component	FIN1001	FIN3001
		Administered 16 days after initiation of r-hFSH treatment at the latest and within 24 hours after criteria for ovulation induction ^b have been met – Utrogestan [®] as luteal support. Given at the day of oocyte retrieval or embryo/blastocyst transfer until after the confirmation of clinical pregnancy up to 35-42 days after oocyte retrieval or upon a negative serum β -hCG test at 16-18 days after oocyte retrieval
Duration of follow-up	Day 38-66	Up to 35-42 days after oocyte retrieval or until child birth/miscarriage
Primary endpoint	AUC ₀₋₁₉₂	Number of oocytes retrieved 34-36 hours after hCG administration
Secondary outcomes	– Pharmacokinetic parameters: eg C _{max} , T _{max} , t _{1/2} – Safety outcomes: eg adverse events and vital signs	– Clinical endpoints: quality of oocytes retrieved, fertilisation rate of oocytes, embryo quality, total dose of r-hFSH required etc – Pregnancy endpoints: implantation rate, clinical pregnancy rate, ongoing pregnancy rate, live birth rate – Safety outcomes: eg adverse events and vital signs
Pre-defined margin	Bioequivalence margin: 90% CI of the ratios of the geometric means of AUC ₀₋₁₉₂ and C _{max} of Bemfola [®] versus Gonal-f [®] within the 80% to 125% margin	Equivalence margin: mean difference of +/- 2.9 in the number of oocytes retrieved between the two treatment arms

AFC = antral follicle count; AUC₀₋₁₉₂ = area under curve from 0 to 192 hours; CI = confidence interval; C_{max} = peak serum concentration; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; OHSS = ovarian hyperstimulation syndrome; POCS = polycystic ovary syndrome; r-hFSH = recombinant human follicle-stimulating hormone; SC = subcutaneously; t_{1/2} = elimination half-life; T_{max} = time to peak serum concentration

^a Defined as fewer than 5 oocytes retrieved in a previous attempt

^b At least one follicle reached a diameter of ≥ 18 mm and two additional follicles reached a diameter of ≥ 16 mm

Source: Table compiled during the evaluation.

- 6.8 When investigating the pharmacokinetics of Bemfola relative to Gonal-f in FIN1001, a single dose of 225IU of the test or reference product was selected, as this dose was in the range of doses used in stimulation protocols for superovulation (150-450IU) where FSH treatment was applied daily for a period of 10-14 days. Treatments with Bemfola and Gonal-f were separated by a washout period of 14 days. The washout period was much longer than the 5 elimination half-lives (around 43 hours) as required by the EMA and the FDA for a crossover design and was sufficient to ensure that drug concentrations were below the lower limit of bioanalytical quantification in all subjects at the beginning of the second treatment period.
- 6.9 FIN1001 specified that, if the 90% confidence intervals (CIs) of the ratios (Bemfola/Gonal-f) of the geometric means for the primary endpoint, i.e. area under serum concentration-time curve from 0 to 192 hours after FSH application (AUC₀₋₁₉₂), and the secondary outcome of peak serum concentration (C_{max}) fell within the interval of 80% to 125%, the two drugs were considered bioequivalent. The acceptance range for bioequivalence as used in the trial is reasonable and is the accepted standard for the evaluation of bioequivalence between two formulations.

- 6.10 In FIN3001, subjects were randomised to receive either Bemfola 150IU daily or Gonal-f 150IU daily for a maximum of 16 days. No dose adjustments were made, except for dose reductions in cases where there was a risk of ovarian hyperstimulation syndrome (OHSS) or other safety concerns. Although the fixed dose regimen specified in the trial cannot reflect clinical practice, where the dosage of follitropin alfa is finely adjusted according to the patient's response, FIN3001 provided comparative data on the relative treatment effect of Bemfola over Gonal-f on an IU to IU basis given the similar total dose of follitropin alfa between the two treatment arms (mean: 1581.8IU Bemfola vs 1582.6IU Gonal-f).
- 6.11 Subjects in the two treatment arms in FIN3001 were comparable in terms of patient characteristics at baseline. The patients enrolled in FIN3001 (mean: 32 years) were younger than women who seek ART in Australia. Demographic data on the Medicare items associated with ART showed that, in 2015, the majority of patients using these services were 35 years or above (62% for MBS item 13200; 75% for MBS item 13201; 73% for MBS item 13202^b). In addition, patients with a high risk of OHSS were not represented in FIN3001, as this trial excluded patients with history/presence of OHSS, polycystic ovary syndrome (PCOS) or an antral follicle count of >20. As these factors affected both treatment arms in FIN3001 the internal validity of the trial result was not compromised.
- 6.12 The primary endpoint in FIN3001 was the number of oocytes retrieved. This is consistent with EMA recommendations on clinical studies that demonstrate comparability of biological medicinal products containing r-hFSH¹ However, the number of oocytes retrieved is an explanatory intermediate endpoint but is not a good predictor of pregnancy. The PBAC has previously accepted the ongoing pregnancy rate (defined as the percentage of women with at least one viable foetus 10 weeks after embryo transfer) as a primary endpoint for the assessment of corifollitropin alfa and Menopur[®] in women participating in an ART program (Menopur Public Summary Document (PSD), March 2012 PBAC meeting; Corifollitropin alfa PSD, November 2010 PBAC meeting). Ongoing pregnancy rate is considered a valid surrogate for live birth. Live birth is the outcome of interest to couples, although it can be argued that the lag time from exposure to the measured outcome (live birth) is an important limitation as it includes multiple factors that could confound or distort the final endpoint of live birth.
- 6.13 FIN3001 assessed the equivalence between Bemfola and Gonal-f in terms of the number of oocytes retrieved. A margin of ± 2.9 oocytes was used for determining whether the difference between the treatment groups was clinically important. The PBAC previously considered a lower margin of -3 oocytes and an upper margin of +5 oocytes as the minimal clinically important difference (MCID) appropriate for patients undergoing ART. Three oocytes are usually required to produce one good quality embryo for transferring (or freezing) and an excess of >5 oocytes is considered undesirable due to the increased risk of developing OHSS (Corifollitropin alfa PSD, November 2010 PBAC meeting). With regard to the MCID for pregnancy rate, the PBAC indicated that, for women undergoing ART, a non-inferiority margin of -8% appeared large in terms of a patient relevant difference in pregnancy rates and

^b Medicare Australia Statistics: medicarestatistics.humanservices.gov.au/statistics/ (Medicare Items processed from January 2015 to December 2015)

considered a difference of $\pm 4\%$ a reasonable MCID in evaluating data on ongoing pregnancy rate (Corifollitropin alfa PSD, March 2013 PBAC meeting).

- 6.14 Both the TGA and the EMA approved Bemfola as a follitropin biosimilar to Gonal-f on the basis of the evidence also presented in the minor submission. An application for Bemfola was submitted to the US FDA. But the FDA required an additional efficacy and safety study in a patient population deemed more appropriate to its requirements. The trial (FIN3002) in progress enrolled patients older than those in FIN3001 (35-42 years vs 20-38 years) and, as requested by the FDA, specified pregnancy rate as the primary endpoint. The ACPM indicated that the requirement of an additional clinical trial by the FDA was based on regulatory requirements in the US as opposed to concerns about efficacy or safety.

Comparative effectiveness

- 6.15 The results of AUC_{0-192} (the primary outcome) and C_{max} reported in FIN1001 are presented in Table 4.

Table 4: Results of AUC_{0-192} and C_{max} in FIN1001, PP and mITT populations^a

Parameter	Geometric means		Ratio of geometric mean (Bemfola [®] vs Gonal-f [®]) ^b	
	Bemfola [®]	Gonal-f [®]	Point estimate	90% CI
AUC_{0-192}	424.9mIU.h/mL	432.7mIU.h/mL	98.2%	[84.7%, 113.9%]
C_{max}	5.69mIU/mL	6.01mIU/mL	94.7%	[89.2%, 100.6%]

AUC_{0-192} = area under curve from 0 to 192 hours; CI = confidence interval; C_{max} = peak serum concentration; mITT = modified intention-to-treat; PP = per protocol

^a Both N=23.

^b Using a method equivalent to fitting an analysis of variance to the primary endpoint, where the factors formulation, period, sequence and subject nested within the sequence were used to explain the overall variability in the observations

Source: Table 2-6, p24 of the minor submission

- 6.16 In FIN1001, the per protocol (PP) and modified intention-to-treat (mITT) analysis sets were identical. Each set excluded two (8%) randomised patients from the pharmacokinetic analysis (1 not receiving treatment and 1 discontinuing treatment due to abnormal ultrasound scan). AUC_{0-192} and C_{max} following application of Bemfola was numerically lower than when Gonal-f was used (424.9mIU.h/mL vs 432.7mIU.h/mL; 5.69mIU/mL vs 6.01mIU/mL). The 90% CI ranged from 0.85 to 1.14 for AUC_{0-192} and from 0.89 to 1.01 for C_{max} , both were within the pre-specified equivalence interval of 0.80-1.25. The minor submission indicated that no significant differences were observed for other pharmacokinetic parameters, eg time to peak serum concentration (T_{max}) and elimination half-life ($t_{1/2}$). The large gap between measurements of follitropin alfa concentration around T_{max} was noted in the TGA Delegate Overview but overall the TGA accepted that there was bioequivalence between Bemfola and Gonal-f.
- 6.17 Results of the number of oocytes retrieved, the primary endpoint, from Trial FIN3001 are presented in Table 5.

Table 5: Results of the number of oocytes retrieved in FIN3001, PP and mITT populations

	Bemfola®	Gonal-f®	T-test TOST Equivalence Analysis	Equivalence Analysis for non- normal data
PP population				
N	N = 243	N = 125	Difference in mean [95% CI]: 0.52 [-0.74, 1.77] ^a ; p-value: 0.0001 ^b	Difference in mean [95% CI]: 0.52 [-0.81, 1.79] ^c ; p-value: 0.0009 ^d
Mean (SD)	11.28 (5.56)	10.77 (6.23)		
Median (range)	11.0 (1, 32)	10.0 (1, 46)		
p-value of test for normality	<0.0001	<0.0001		
mITT population				
N	N = 272	N = 135	Difference in mean [95% CI]: 0.46 [-0.79, 0.72] ^a ; p-value: <0.0001 ^b	Difference in mean [95% CI]: 0.46 [-0.90, 1.67] ^c ; p-value: 0.0006 ^d
Mean (SD)	11.03 (5.96)	10.56 (6.30)		
Median (range)	10.0 (0, 32)	10.0 (0, 46)		
p-value of test for normality	<0.0001	<0.0001		

CI = confidence interval; mITT = modified intention-to-treat; PP = per protocol; SD = standard deviation

^a Using Schuirmann's TOST test

^b Using Pooled method. Larger of the two one-sided p-values

^c Using bootstrap-t approach

^d Using Mann-Whitney U test. Larger of the two one-sided p-values

Source: Table 2-14, p42 of the minor submission

- 6.18 The mean numbers of oocytes retrieved in the PP population of the Bemfola and Gonal-f treatment groups were 11.28 and 10.77, respectively. In the PP population, the difference in the mean number of oocytes retrieved between the two treatment groups was 0.52, with a bootstrap-t 95% CI of [-0.81, 1.79] (this method was used due to the non-normality of the distribution of the primary endpoint). The equivalence analysis using the Mann-Whitney U test was significant for both one-sided tests of the null hypothesis (p-values = 0.0009). Similar results were reported in the mITT population (defined as all randomised patients having received at least one administration of the study treatment and with data for analysis of the primary outcome). The equivalence of the treatment groups regarding the number of oocytes retrieved was achieved for both study populations, using an equivalence margin of ± 2.9 . The 95% CI (-0.81, 1.79) was within the non-inferiority margin previously accepted by the PBAC (-3, +5). The robustness of this result was confirmed by Schuirmann's TOST test.
- 6.19 Table 6 presents the patient-relevant pregnancy outcomes (secondary efficacy endpoints) in FIN3001.

Table 6: Results of pregnancy rates in FIN3001, PP and mITT populations

	Bemfola® n/N (%)	Gonal-f® n/N (%)	RD [95% CI]^a	RR [95% CI]^a
PP population^b				
Patients undergoing embryo transfer	██████ (██████%)	██████ (██████%)	██████% [-██████%, ██████%]	██████
Biochemical pregnancy ^{c,d}	██████ (██████%)	██████ (██████%)	██████% [-██████%, ██████%]	██████
Ongoing pregnancy ^{c,e}	██████ (██████%)	██████ (██████%)	██████% [-██████%, ██████%]	██████
Live born children ^c	██████ (██████%)	██████ (██████%)	██████% [-██████%, ██████%]	██████
mITT population				
Patients undergoing embryo transfer	██████ (██████%)	██████ (██████%)	██████% [-██████%, ██████%]	██████
Biochemical pregnancy ^{c,d}	██████ (██████%)	██████ (██████%)	██████% [-██████%, ██████%]	██████
Ongoing pregnancy ^{c,e}	██████ (██████%)	██████ (██████%)	██████% [-██████%, ██████%]	██████
Live born children ^c	██████ (██████%)	██████ (██████%)	██████% [-██████%, ██████%]	██████

CI = confidence interval; mITT = modified intention-to-treat; PP = per protocol; RD = risk difference; RR = relative risk

^a RDs and RRs were calculated using Stata®13.1

^b Results of PP analyses were extracted from the clinical study report (Table ES08T, pp204-205) during the evaluation

^c Percentages were based on the number of patients undergoing embryo transfer

^d Biochemical pregnancy was defined as a positive serum test for β-hCG (>10U/l) 16-18 days after oocyte retrieval.

^e Ongoing pregnancy was defined as presence of at least one viable foetus 10 weeks after embryo transfer documented by ultrasound.

Source: Table 2-23, p49 of the minor submission

6.20 In both PP and mITT populations, the ongoing pregnancy rate and live birth rate in women undergoing embryo transfer were numerically lower in those receiving 150IU Bemfola when compared to the Gonal-f group. The lower bound of the 95% CI (-16.2%) in the PP population was below the non-inferiority margin previously accepted by the PBAC (-4%). The wide confidence interval suggests that the analysis was not sufficiently powered.

6.21 In FIN3001, patients who did not get pregnant after a completed first cycle of Bemfola/Gonal-f treatment and ART could undergo a second fresh cycle of r-hFSH treatment. Results of treatment Cycle 2 were not provided in the minor submission.

Comparative harms

6.22 Results of adverse events (AEs) in FIN3001 are presented in Table 7. No comparative safety data were reported in FIN1001.

Table 7: Overview of AEs in FIN3001

	Bemfola® (N = 275)	Gonal-f® (N = 135)	RD [95% CI]^a	RR [95% CI]^a
Any AEs	203 (73.8%)	92 (68.1%)	5.7% [-3.8%, 15.1%]	1.08 [0.95, 1.24]
Drug-related AEs	180 (65.5%)	75 (55.6%)	9.9% [-0.2%, 20.0%]	1.18 [0.99, 1.40]
Serious AEs	11 (4.0%)	3 (2.2%)	1.8% [-1.6%, 5.2%]	1.80 [0.51, 6.35]
Drug-related serious AEs	8 (2.9%)	2 (1.5%)	1.4% [-1.4%, 4.3%]	1.96 [0.42, 9.12]
Severe AEs	17 (6.2%)	7 (5.2%)	1.0% [-3.7%, 5.7%]	1.19 [0.51, 2.81]
Drug-related severe AEs	13 (4.7%)	5 (3.7%)	1.0% [-3.0%, 5.1%]	1.28 [0.46, 3.51]
AEs leading to discontinuation	11 (4.0%)	1 (0.7%)	3.3% [0.5%, 6.0%]	5.40 [0.70, 41.40]
Drug-related AEs leading to discontinuation	10 (3.6%)	1 (0.7%)	2.9% [0.3%, 5.5%]	4.91 [0.63, 37.96]
Deaths	0 (0.0%)	0 (0.0%)	–	–

AE = adverse event; CI = confidence interval; RD = risk difference; RR = relative risk

^a RDs and RRs were calculated during the evaluation

Source: Table 2-24, p49 of the minor submission

- 6.23 AEs and treatment-related AEs were more common in the Bemfola group than in the Gonal-f group (73.8% vs 68.1% and 65.5% vs 55.6%, respectively). Bemfola was associated with a slightly higher incidence of serious AEs (4.0% vs 2.2%). The risk of discontinuing due to an adverse event in the Bemfola treatment arm was more than 5 times the risk in the Gonal-f arm (4.0% vs 0.7%), although absolute differences were small.
- 6.24 Table 8 reports on the incidence and severity of OHSS in FIN3001. OHSS is an AE of concern when assessing medicines aimed at controlled ovarian hyperstimulation in women undergoing ART.

Table 8: OHSS rates in FIN3001

	Bemfola® (N = 275)	Gonal-f® (N = 135)	RD [95% CI]^a	RR [95% CI]^a
Any OHSS	64 (23.3%)	18 (13.3%)	9.9% [2.3%, 17.5%]	1.75 [1.08, 2.82]
OHSS grade ^b				
Mild	40 (14.5%)	14 (10.4%)	4.2% [-2.4%, 10.8%]	1.40 [0.79, 2.49]
Moderate	22 (8.0%)	5 (3.7%)	4.3% [-0.2%, 8.8%]	2.16 [0.84, 5.58]
Severe	2 (0.7%)	1 (0.7%)	0.0% [-1.8%, 1.7%]	0.98 [0.09, 10.73]
Serious ^c	8 (2.9%)	2 (1.5%)	1.4% [-1.4%, 4.3%]	1.96 [0.42, 9.12]
Threatened	49 (17.8%)	16 (11.9%)	6.0% [-1.1%, 13.1%]	1.50 [0.89, 2.54]
Dose reduction due to OHSS	32 (11.6%)	10 (7.4%)	4.2% [-1.6%, 10%]	1.57 [0.8, 3.1]
Treatment discontinuation due to OHSS	9 (3.3%)	1 (0.7%)	2.5% [0%, 5.1%]	4.42 [0.57, 34.52]

CI = confidence interval; OHSS = ovarian hyperstimulation syndrome; RD = risk difference; RR = relative risk

^a RDs and RRs were calculated during the evaluation.

^b OHSS was graded according to the recommendations of the Practice Committee of the American Society for Reproductive Medicine Mild – mild manifestations of OHSS include transient lower abdominal discomfort, mild nausea, vomiting, diarrhoea and abdominal distension. Moderate - mild manifestations of OHSS that persisted, worsened, or included ascites. Severe - serious manifestations of OHSS existed when pain is accompanied by one or more of the following: rapid weight gain, tense ascites, haemodynamic instability (orthostatic hypotension, tachycardia); respiratory difficulty (tachypnoea); progression of oliguria, laboratory abnormalities.

^c AEs resulting in death, life-threatening, inpatient hospitalisation, persistent or significant disability/incapacity or other medically important events.

Source: Table 53, p117; Table 54, p117; Table 56, p119; and Table 58, p123 of the clinical study report

- 6.25 The incidence of OHSS was statistically significantly higher in patients receiving Bemfola compared to patients treated with Gonal-f (23.3% vs 13.3%; RD: 9.9% [2.3%, 17.5%]), with the majority of these OHSS cases reported as “threatened” OHSS (17.8% vs 11.9%). The definition of “threatened” OHSS was not provided in the clinical study report. Serious OHSS^c and severe manifestations of OHSS, classified based on the recommendations of the Practice Committee of the American Society for Reproductive Medicine, were relatively uncommon in both FIN3001 treatment arms (Bemfola vs Gonal-f: ■■■% vs ■■■% and 0.7% vs 0.7%, respectively).
- 6.26 The higher incidence of overall AEs and OHSS in the Bemfola arm was noted by the TGA Delegate. The Delegate stated that these results could be due to potential biases, differences in potency and/or device between Bemfola and Gonal-f, etc. It was also noted that in clinical practice, women receiving follitropin alfa are closely monitored for OHSS and that strategies to prevent adverse outcomes are available. The Delegate requested advice in relation to this issue. The ACPM advised that the rate of OHSS reported in FIN3001 was higher than that in clinical practice, where around 4-6% of women undergoing IVF develop OHSS, and that OHSS is clinically manageable in Australian practice.
- 6.27 Data on immunogenicity were extracted from the FIN3001 clinical study report as they were not reported in the minor submission. The mean immunogenicity (relRU) was similar in the two treatment arms at baseline (■■■ (standard deviation (SD): ■■■) relRU vs ■■■ (SD: ■■■) relRU). No remarkable changes were observed over time. Analysis of antibodies specific for Bemfola or Gonal-f indicated there was no evidence of immunogenicity (ie antibody reactivity to Bemfola or Gonal-f) in either treatment group.

Clinical claim

- 6.28 The minor submission claimed that Bemfola is bioequivalent to Gonal-f and has comparative effectiveness and safety in females undergoing superovulation for the purpose of ART.
- 6.29 The bioequivalence claim is supported by the pharmacokinetic data from FIN1001 which showed that 90% CIs of the ratios of AUC_{0-192} and C_{max} for Bemfola versus Gonal-f were within the required bioequivalence range of 80%-125%.
- 6.30 The PBAC noted that the TGA has declared Bemfola a biosimilar to Gonal-f. Therefore, the claim of bioequivalence was appropriate.

Economic analysis

- 6.31 The minor submission did not present a formal economic analysis. However, a cost-minimisation approach was implied as Bemfola was priced on an IU to IU basis with Gonal-f. The statutory 16% price reduction for Gonal-f has been taken into

^c AEs resulting in death, life-threatening, hospitalisation, persistent or significant disability/incapacity or other medically important events

account in calculating the ex-manufacturer price for Bemfola assuming Bemfola will be listed on the PBS as the first bioequivalent or biosimilar to Gonal-f.

- 6.32 Drug wastage was not considered when determining the price for Bemfola. Bemfola has a formulation intended for single use; whereas Gonal-f is intended for multiple injections. This has implications for drug wastage when dose adjustment is needed. For example, if a woman uses the 225 IU Bemfola pre-filled pen and requires a dose increase or dose decrease, she will need to be given a different pen, e.g. 150 IU, 300 IU or 450 IU. This is not necessary when using Gonal-f, as multiple different doses can be administered with the same pen within 21 days after opening. Consequently, with the single-use system, more unused Bemfola will be discarded. In addition, the maximum amount of follitropin alfa is generally higher for Bemfola compared to Gonal-f. This is particularly important given the flexible dosing and treatment duration of follitropin alfa therapy, which may lead to increased drug wastage for Bemfola relative to Gonal-f. When the PBAC considered Menopur (human menopausal gonadotrophin (hMG)) at the March 2012 meeting, the Committee considered that the price of Menopur “should factor in a percentage wastage for drug loss related to the mode of administration and vial strengths” (p6, Menopur PSD, March 2012 PBAC meeting).
- 6.33 The Pre-PBAC Response (p.2) argued that it was highly unlikely that Bemfola would result in more drug wastage in clinical practice compared with Gonal-f and that for ART, the “standard treatment protocol is informed by the tests performed prior to initiating treatment. Subsequent adjustments to the treatment protocol are made on a case by case basis, but are generally not necessary.” The Pre-PBAC Response further proposed that anecdotal evidence suggests that the majority of prescriptions of Gonal-f are dispensed for the maximum dose and quantity, and therefore “the Gonal-f multi-use pen facilitates overprescribing with any unused drug discarded.”

Drug cost/patient/cycle: \$ [REDACTED]

- 6.34 As the average dose of Bemfola varies significantly for individual patients and patients may undertake more than one cycle of ART per year, the drug cost/patient/year is difficult to determine. However as Bemfola is priced on a cost per IU of \$ [REDACTED] (approved ex-manufacturer price). For patients undergoing ART, an average cost per cycle can be estimated using the average dose from FIN3001 (1581.8IU). $\$ [REDACTED] \times 1581.8 = \$ [REDACTED]$ per patient/cycle (excluding any wastage). The minor submission did not provide any information on the average cost / dose / patient / year for anovulatory infertility and hypogonadotrophic hypogonadism.

Estimated PBS usage & financial implications

- 6.35 The minor submission estimated a net cost saving to the PBS of \$20-\$30 million in Year 5 of listing, with a total net saving to the PBS of more than \$100 million over the first five years of listing. This is summarised in Table 9.

Table 9: Net financial implications to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Net costs to the PBS/RPBS from anovulatory infertility					
Cost to the PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Patient co-payments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Total cost to the PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net costs to the PBS/RPBS from hypogonadotrophic hypogonadism					
Cost to the PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Patient co-payments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Total cost to the PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to the PBS/RPBS from assisted reproductive technology (ART)					
Cost to the PBS/RPBS	-\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	\$ [REDACTED]
Patient co-payments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Total cost to the PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	\$ [REDACTED]
Net financial implications					
Net cost to the PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net patient co-payments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net financial implications	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]

Source: Table 3-14, p72 of the submission

- 6.36 Approximately half of the cost savings associated with the proposed listing of Bemfola are associated with the statutory 16% price reduction, with the remaining being attributed to differences in the number of prescriptions required. The submissions' estimates do not consider wastage. As highlighted above, the Bemfola formulation is intended for single use; while Gonal-f is supplied as multi-dose pen. It is possible that the use of Bemfola may result in more wastage relative to Gonal-f due to dose adjustment and unused Bemfola being discarded. Furthermore, the submission's assumption that all patients will be dispensed the maximum quantity of Bemfola is unlikely to occur in practice and overestimates the cost savings to the PBS.
- 6.37 The Pre-PBAC Response (p.3) contended that a recent study, a retrospective analysis of Gonal-f and Bemfola prescription and usage data in the United Kingdom, supported an assertion that there would be reduced wastage with Bemfola compared to Gonal-f. However the PBAC considered that it was difficult to interpret the retrospective analysis in this context as there was uncertainty around how much Bemfola would actually have been supplied.

Quality use of medicines

- 6.38 The postulated advantages of Bemfola over Gonal-f include: i) a preservative-free formulation; ii) convenience and accurate dosage due to the device of a small single-use pen with volume and injection control mechanisms; and iii) allowance for fine tune dosing (minimum 12.5IU increments vs 37.5IU for Gonal-f). The smaller dosage adjustment claimed to be possible with Bemfola could be advantageous in the ovarian stimulation ART protocol, but not in the other proposed indications where the dose of r-hFSH (including Bemfola and Gonal-f) is adjusted in

increments/decrements of 37.5IU up to 75IU to obtain an adequate, but not excessive response.

- 6.39 Patients requiring dose adjustment may need to switch to a different strength of the Bemfola pen; whilst the Gonal-f pen allows for multiple administrations of different doses of Gonal-f and is likely to reduce drug wastage.
- 6.40 Bemfola and Gonal-f differ in their presentations: Bemfola is a single dose pen and Gonal-f a multidose pen; only two strengths of the brands are the same (300 IU and 450 IU) and the proposed PBS maximum quantities differ. Patients switching from one medicine to the other would require education regarding the two medications and their associated injection devices.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of follitropin alfa (Bemfola) as a biosimilar of follitropin alfa (Gonal-f), on a cost-minimisation basis to follitropin alfa (Gonal-f), where the equi-effective doses are 1.0 I.U follitropin alfa (Bemfola) and 1.0 I.U follitropin alfa (Gonal-f). The PBAC recommended that the same indications that apply to follitropin alfa (Gonal-f) should apply to follitropin alfa (Bemfola). Gonal-f is currently listed on the General Schedule for anovulatory infertility and hypogonadotrophic hypogonadism, and on the Section 100 IVF Program for Assisted Reproductive Technology.
- 7.2 The PBAC considered that a claim of non-inferior comparative effectiveness and non-inferior comparative safety was adequately supported. The PBAC noted that the TGA has declared Bemfola a biosimilar to Gonal-f.
- 7.3 The PBAC advised the Minister that it considered the Gonal-f and Bemfola brands of follitropin alfa could not be marked as equivalent in the Schedule of Pharmaceutical Benefits ("a" flagged), for the purposes of substitution by the pharmacist at the point of dispensing. The PBAC advised that this is primarily due to differences in the strengths, number of pens per pack and maximum quantities between the brands, which make substitution at the pharmacy level difficult from a practical perspective.
- 7.4 The PBAC considered a range of other factors in forming its view on brand substitution ("a" flagging) including:
- The results from randomised clinical trials FIN1001, with regard to pharmacokinetic bioequivalence, and FIN3001, with regard to oocyte retrieval, support a finding that Bemfola has equivalent effectiveness and equivalent safety compared to Gonal-f.
 - Subjects in FIN3001, i.e. women receiving ART, may be the most "sensitive" population to identify differences, if any, in the benefits and harms associated with Bemfola with Gonal-f.
 - FIN3001 excluded patients who had received more than one previous treatment cycle. Whilst the number of previous treatment cycles, if any, was not recorded, it is possible that some patients in this trial were treatment-naïve. Results were not separately reported for these patients.

- The submission did not provide any evidence regarding the efficacy and safety of switching patients between Bemfola and Gonal-f or vice versa.
 - The TGA has declared Bemfola a biosimilar to Gonal-f.
- 7.5 The PBAC noted that the submission estimated net overall savings to the PBS of approximately more than \$100 million over the first five years of listing. Approximately half of this was based on the impact of the statutory 16% price reduction following the listing of a biosimilar brand. The remaining savings were attributed to differences in the number of prescriptions, which the PBAC considered may not be plausible. The PBAC further considered that accounting for potential wastage, the estimated savings may be overestimated. The PBAC advised that the Department should take into account increased wastage associated with Bemfola when negotiating the price.
- 7.6 The PBAC recommended minor amendments to the requested restriction as per the wording in the recommended listing below. The PBAC noted that these changes would also apply to the current Gonal-f restrictions.
- 7.7 The PBAC advised that Bemfola 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.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty Units	No. of Rpts	Proprietary Manufacturer	Name and
FOLLITROPIN ALFA 75 units (5.5 microgram)/0.125 mL injection, 5 x 0.125 mL injection devices	15	0	Bemfola®	FINOX Biotech Australia
150 units (11 microgram)/0.25 mL injection, 5 x 0.25 mL injection devices	15	0		
225 units (16.5 microgram)/0.375 mL injection, 5 x 0.375 mL injection devices	15	0		
300 units (22 microgram)/0.5 mL injection, 5 x 0.5 mL injection devices	15	0		
450 units (33 microgram)/0.75 mL injection, 5 x 0.75 mL injection devices	15	0		

Category / Program	Section 100 – IVF
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives

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Condition:	Assisted Reproductive Technology
PBS Indication:	Assisted Reproductive Technology
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must be receiving medical services as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule

Name, Restriction, Manner of administration and form	Max. Qty Units	№.of Rpts	Proprietary and Manufacturer	Name
FOLLITROPIN ALFA 75 units (5.5 microgram)/0.125 mL injection, 5 x 0.125 mL injection devices	15	1	Bemfola®	FINOX Biotech Australia
150 units (11 microgram)/0.25 mL injection, 5 x 0.25 mL injection devices	15	1		
225 units (16.5 microgram)/0.375 mL injection, 5 x 0.375 mL injection devices	15	1		

Category / Program	Section 85
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Anovulatory infertility
PBS Indication:	Anovulatory infertility
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Administrative Advice	<p>NOTE: Except in cases of hypopituitarism or primary amenorrhoea, the patient should have been adequately treated with clomiphene citrate and/or gonadorelin and failed to have conceived. Women who have had apparent ovulation induced by other agents and have failed to conceive should have laparoscopic evidence that there is no other impediment to conception. Oligomenorrhoea should have been present for at least twelve months or amenorrhoea for at least six months prior to treatment. Patients with hyperprolactinaemia should have had appropriate surgical or medical treatment prior to treatment.</p>

Condition:	Infertility
PBS Indication:	Infertility

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Clinical criteria	The condition must be due to hypogonadotrophic hypogonadism, AND The treatment must be following failure of 6 months' treatment with human chorionic gonadotrophin to achieve adequate spermatogenesis, AND The treatment must be administered with human chorionic gonadotrophin.
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Administrative Advice	NOTE: Except in cases of hypopituitarism or primary amenorrhoea, the patient should have been adequately treated with clomiphene citrate and/or gonadorelin and failed to have conceived. Patients with hyperprolactinaemia should have had appropriate surgical or medical treatment prior to treatment.

8 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.

9 Sponsor's Comment

FINOX welcomes the PBAC's positive recommendation to list Bemfola on the PBS. FINOX did not apply to the PBAC for a-flagging of Bemfola with Gonal-f due to differences in the prescribing and dispensing patterns with the two forms of follitropin alfa in Australia.