

## 11.02 FOLLITROPIN ALFA

**Injection 300 I.U. in 0.5 mL multi-dose cartridge,  
Injection 450 I.U. in 0.75 mL multi-dose cartridge,  
Injection 900 I.U. in 1.5 mL multi-dose cartridge,  
Gonal-f® Pen  
Merck Healthcare Australia Pty Ltd**

### 1 Purpose of submission

- 1.1 The Category 2 submission requested a price increase for Gonal-f® Pen (herein referred to as Gonal-f) based on the therapeutic relativities of Gonal-f compared to biosimilar follitropin alfa products. Gonal-f is listed in Section 100 (In Vitro Fertilisation (IVF) Program) for the treatment of women who are undergoing assisted reproductive technology (ART).
- 1.2 The basis of the requested price increase was a cost-effectiveness analysis versus biosimilar preparations of follitropin alfa.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

Component	Description
Population	Patients who are undergoing ART Patient must be receiving medical services as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule <sup>1</sup>
Intervention	Follitropin alfa (Gonal-f)
Comparator	Biosimilar preparations of follitropin alfa (Bemfola, Ovaleap, Primapur and Follitrope) – Bemfola was nominated as a proxy in the economic evaluation
Outcomes	1) Clinical pregnancy rate 2) Ongoing pregnancy rate 3) Live birth rate
Clinical claim	The submission described Gonal-f as superior in terms of effectiveness for fertility treatment compared with biosimilar preparations of follitropin alfa and non-inferior in terms of safety compared to the biosimilars.

Source: Compiled during the evaluation from pp 11-12, 33 of the submission; ART = assisted reproductive technology

- 1.3 Additionally, the submission requested that Gonal-f should not be marked as equivalent to Ovaleap in the Pharmaceutical Benefits Scheme (PBS) Schedule ('a-flagged') for the purpose of substitution by the pharmacist at the point of dispensing.

## 2 Background

### Registration status

2.1 Gonal-f was approved and registered by the Therapeutic Goods Administration (TGA) in 1998 for the following indications for:

- the treatment of anovulatory infertility in women who have been unresponsive to clomiphene citrate or where clomiphene citrate is contraindicated
- controlled ovarian hyperstimulation in women undergoing assist reproductive technologies
- use with concomitant human chorionic gonadotrophin (hCG) therapy for the stimulation of spermatogenesis in gonadotrophin-deficient men in whom hCG alone is ineffective.

### Previous PBAC consideration

2.2 The originator brand of follitropin alfa, Gonal-f, was considered by the PBAC in December 1997 and listed on 1 April 1998.

2.3 Bemfola, the first follitropin alfa biosimilar drug, was recommended at the March 2016 PBAC meeting and listed on 1 August 2016. The PBAC advised that the Gonal-f and Bemfola brands of follitropin alfa could not be marked as equivalent (“a” flagged) for the purposes of substitution, primarily due to differences in the strengths, number of pens per pack and maximum quantities between the brands which make substitution at the point of dispensing impractical.

2.4 Ovaleap, a second follitropin alfa biosimilar drug, was recommended at the July 2021 PBAC meeting. The PBAC considered Ovaleap as equivalent for the purposes of substitution with Gonal-F as the issues applying to Bemfola do not apply to Ovaleap.

## 3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
follitropin alfa, injection, 300iu 0.5mL pen device	2	0	Current \$234.84 Requested \$ [REDACTED]	Gonal-f Pen Merck Healthcare Australia Pty Ltd
follitropin alfa, injection, 450iu 0.75mL pen device	2	0	Current \$348.36 Requested \$ [REDACTED]	
follitropin alfa, injection, 900iu 1.5mL pen device	5	0	Current \$1685.18 Requested \$ [REDACTED]	

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

Source: Compiled during the evaluation from PBS online and the submission requested price

- 3.1 The submission requested a price increase for Gonal-f, but no changes to the restrictions of the current PBS listings. The Pre-Sub-Committee Response (PSCR) clarified that the proposed DPMQ used in the submission was based on reversing all the price reductions that have occurred since Gonal-f moved to the F2 formulary after the listing of Bemfola to achieve the prior F1 price, that is, the reversal of a 16% price reduction as well as the impacts of subsequent reference pricing. The PBAC noted that the submission requested an approximate 25% increase to the current price of Gonal-f:
- 300 IU 0.5mL pen device from \$234.84 to a requested price of \$ [REDACTED] ([REDACTED]% increase)
  - 450 IU 0.75mL pen device from \$348.36 to a requested price of \$ [REDACTED] ([REDACTED]% increase)
  - 900 IU 1.5mL pen device from \$1685.18 to a requested price of \$ [REDACTED] ([REDACTED]% increase).
- 3.2 The submission argued that Gonal-f is therapeutically distinct from other follitropin alfa biosimilars and therefore Gonal-f is not clinically interchangeable with other biosimilars. The PSCR stated that the clinical evidence from the Chua et al. (2021) meta-analysis was supportive of the submission’s clinical claim that Gonal-f is superior to the biosimilar preparations.
- 3.3 The PBAC noted that a claim of superior effectiveness of the reference brand to the biosimilar brand is contradictory to the decision made by the TGA and other national/regional Regulatory Agencies (e.g., European Medicines Agency) under the biosimilar regulatory framework. Regulatory evaluations of biosimilar medicines place an emphasis on the pre-clinical data (also referred to as in-vitro or analytic data). In-vitro characterisation of the molecule is the pivotal evidence used to establish that a proposed biosimilar is highly similar to the reference biological medicine because it is the most sensitive way of identifying differences between the biosimilar and the reference biological medicine. The PBAC noted that the TGA determined via independent, rigorous, and comprehensive evaluations, that other follitropin alfa products are biosimilar to the reference brand, Gonal-f. The PBAC considered that the submission did not include the necessary information on in-vitro characteristics of the biosimilars versus Gonal-f. The PBAC considered that a totality of evidence approach, which would include the in-vitro characterisation of the molecule, pharmacokinetic analyses and randomised clinical endpoint trials, would be required to support the submission’s clinical claim.
- 3.4 Based on the above views, the PBAC considered that Ovaleap and Gonal-f be marked as equivalent for the purposes of substitution. Furthermore, the PBAC recalled in its July 2021 consideration of Ovaleap that in practice the prescribing clinician would have the option to specify “No Brand Substitution Permitted” should they wish to

prescribe a particular brand. Pharmacists have a responsibility to adhere to these directions where specified.

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

## **4 Population and disease**

- 4.1 The target population in the submission was patients undergoing ART requiring controlled ovarian stimulation. The most recent national estimates indicate that 4.9% of all women who gave birth in Australia in 2018 received some form of ART treatment.
- 4.2 Follitropin alfa is the synthetic form of follicle stimulating hormone (FSH), a pituitary glycoprotein hormone which is a regulator of reproductive function in both females and males; specifically, it initiates ovarian follicular development and spermatogenesis. The rationale for its clinical use is the activation of these biological functions in patients with a variety of fertility problems. The PBAC noted that ovarian follicular development and spermatogenesis are contributing factors to the success of infertility treatment, and that it has previously considered live birth to be the most patient-relevant outcome.
- 4.3 The follitropin alfa regimen involves the administration of 150 IU to 225 IU of Gonal-f daily, commencing on days 2 or 3 of the IVF cycle. Treatment continues until adequate follicular development is achieved; doses are adjusted according to the patient's response, but usually not higher than 450 IU daily. A single injection of hCG is administered 24–48 hours after the last Gonal-f injection to induce final follicular maturation. Down-regulation with either a gonadotropin-releasing hormone (GnRH) agonist or antagonist is now commonly used to suppress the endogenous luteinizing hormone surge and to control toxic levels of luteinizing hormone.

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

## **5 Comparator**

- 5.1 The submission nominated “biosimilar preparations of follitropin alfa” as the comparator. The clinical evaluation included all biosimilar preparations of follitropin alfa as comparators including Bemfola, Ovaleap, Primapur and Follitrope. As Primapur and Follitrope are not currently approved by the TGA, the submission presented a separate analysis including only Bemfola and Ovaleap as comparators. The PBAC considered that this was appropriate.
- 5.2 Bemfola was used as a proxy for all biosimilar preparations of follitropin alfa in the economic evaluation and financial estimates; Bemfola was selected as a proxy because it is currently PBS listed.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician presented a commentary on the methodology of the Chua et al. 2021 systematic review and meta-analysis, and explained the choice and relevance of the outcomes presented. The clinician was supportive of the submission's claim that Gonal-f is superior to its comparators but noted that further research is required to determine the nature of the superiority and the mechanism by which it is achieved. The PBAC considered that the hearing provided a greater insight into how the meta-analysis was conducted. The PBAC did not ask the clinician any questions.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (6) and organisations (2) via the Consumer Comments facility on the PBS website. The PBAC noted the advice received from Fertility First and Access Australia as well as the other consumer comments that did not support the 'a'-flagging of Ovaleap with Gonal-f. The comments described a range of concerns about the pharmaceutical and clinical differences affecting patient outcomes, and quality use of medicine issues. Notably a comment described the specifying of "Brand Substitution Not Permitted" as an administrative burden for prescribers and that 'a' flagging Gonal-f to Ovaleap allowed a margin for error. The PBAC noted that at the time the Consumer Comments facility closed for this submission, the Public Summary Document (PSD) for Ovaleap had not yet been made publicly available.

### ***Clinical trials***

- 6.3 The submission was based on a systematic review and meta-analysis by Chua et al. 2021 which included five head-to-head randomised trials comparing Gonal-f to biosimilar preparations of follitropin alfa (n=1,181; corrected to n=2,332 during the evaluation as the reported sample size in the submission was less than the sum of the sample sizes of the included trials). Brand-specific analyses were conducted by the specific biosimilar preparation used including Bemfola (n=1,472, 2 studies), Ovaleap (n=299, 1 study), Primapur (n=110, 1 study), and Follitrope (n=451, 1 study). The qualitative systematic review used information from 17 trials while the meta-analysis used the data from five published randomised trials. This review was funded by the sponsor of Gonal-f.
- 6.4 Details of the trials presented in the submission are provided in Table 2.

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

Trial ID/Author Year	Protocol title/ Publication title	Publication citation
NCT01121666	A multi-Centre phase 3 trial comparing efficacy and safety of Bemfola ® versus Gonal-f ® in women undergoing ovarian stimulation for IVF	Reprod BioMed Online. 2015;30:504-13
NCT01687712	Fertility Biotech AG: Phase III Trial Comparing Efficacy and Safety of AFOLIA vs Gonal-f RFF in Women (35 to 42) Undergoing IVF	U.S. National Library of Medicine; 2012 September. Report No.: NCT1687712
ISRCTN74772901	Strowitzki T, Kuczynski W, Mueller A, Bias P. Randomized, active-controlled, comparative phase 3 efficacy and safety equivalence trial of Ovaleap ® (recombinant human follicle-stimulating hormone) in infertile women using assisted reproduction technology (ART)	Reprod Biol Endocrinol. 2016;14:1
	Strowitzki T, Kuczynski W, Mueller A, Bias P. Safety and efficacy of Ovaleap® (recombinant human follicle-stimulating hormone) for up to 3 cycles in infertile women using assisted reproductive technology: a phase 3 open-label follow-up to Main trial.	Reprod Biol Endocrinol. 2016;14:31
NCT03088137	A multicentre, randomized, phase III trial comparing the efficacy and safety of follitropin alfa biosimilar and the original follitropin alfa	Eu J Obstet Gynecol Reprod Biol. 2019;241:6-12
NCT03506243	Efficacy and safety of recombinant human follicle-stimulating hormone in patients undergoing in vitro fertilization-embryo transfer	Aging (Albany NY). 2020;12:4918-30

Source: Table 3, p23 of the submission.

- 6.5 The submission identified another relevant meta-analysis, Papsch et al. 2018<sup>2</sup>, which was a post-hoc analysis of Phase III clinical trial data for Ovaleap and Bemfola compared with Gonal-f that did not consider other biosimilar preparations. However, this was not assessed in the submission because it was a non-peer reviewed poster presented at ISPOR Europe 2018. The PBAC considered that this was an appropriate exclusion.
- 6.6 The submission presented live birth rate as the primary outcome since it was the PBAC’s preferred outcome in its recommendation of Luveris (paragraph 7.8, Luveris, PSD, March 2015 meeting). The PBAC noted that Luveris was the originator and only brand of lutropin alfa, and as such, the evidence and claim for Luveris was therefore in relation to establishing clinical and cost effectiveness, rather than a claim in relation to biosimilarity. The submission also presented the following additional outcomes to substantiate the superiority of Gonal-f over the follitropin alfa biosimilar preparations: ongoing pregnancy rate, cumulative live birth, cumulative clinical pregnancy, and cumulative ongoing pregnancy. The evaluation questioned the appropriateness of the outcomes used in the submission given that the trials were not powered to detect differences in live birth rates and the other outcomes, noting that the trials’ primary outcome of number of oocytes retrieved was not included in the submission. Additionally, the evaluation noted that the trials were designed and powered to establish the non-inferiority of Gonal-f to follitropin alfa biosimilar preparations. The PSCR stated that the rationale for the Chua et al. (2021) meta-analysis was to study

<sup>2</sup> Papsch R, Roeder C, D'Hooghe T, Longobardi S. PMU40-live birth rate (LBR), ongoing pregnancy rate (OPR) and ovarian hyperstimulation syndrome (OHSS) risk with originator versus biosimilar recombinant follitropin ALFA: a pooled analysis of clinical trial data. Value in Health. 2018 Oct 1;21:S314-5.

the outcome of live birth rate and cumulative live birth rate per started cycle which are more clinically relevant than just the number of oocytes retrieved. The PSCR noted that this was aligned with the European Society of Human Reproduction and Embryology (ESHRE) Guideline for Ovarian Stimulation in IVF/ICSI and the International Committee for Monitoring Assisted Reproductive Technology (ICMART), both of which state that the most relevant outcomes of infertility treatment are live birth rate and cumulative live birth rate. While the PBAC agreed with the submission that the live birth rate was a patient-relevant outcome, it noted that the mechanism of action of follitropin alfa relates to oocyte retrieval and thus this is the appropriate outcome to measure comparative effectiveness. Additionally, the PBAC noted that other factors contribute to the number of live births (e.g., skill of the embryologist and selection of which embryos to transfer) and considered it was not biologically or clinically plausible that differences in live births would be due to follitropin alfa alone.

- 6.7 The submission included only the results of the first cycles of treatment in the randomised trials and no justification was provided for excluding results from additional cycles of treatment when available. The PSCR clarified that the first cycle contributed to the primary end point of live birth and reflected the most comprehensive and homogeneous data included in the five trials. The PSCR noted that subsequent cycles contributed to cumulative secondary outcomes and were not ignored, but rather could not be included for accurate comparative purposes.
- 6.8 The PBAC considered that the submission provided inadequate detail on the relevant direct randomised trials included in the meta-analysis. There was no information on the characteristics of patients who were lost to follow-up, patients who withdrew or patients who missed an assessment. Additionally, the PBAC considered it is likely that the target population in Australia would have characteristics of those who were excluded in this trial, especially around the history of access to ART and miscarriage.
- 6.9 The average ages of patients who use ART in Australia is 35.8 years for women using their own oocytes and embryo, and 40.3 years for those receiving oocytes or embryo. The mean age of the participants in the five randomised trials was 32.3 years (3.5 years younger than the Australian population receiving ART treatment, on average). The PBAC considered that the effectiveness of Gonal-f for the Australian population may be lower than what was observed in the trials.
- 6.10 The submission evaluated the risk of bias, for the pre-specified primary endpoint of number of oocytes, as low in four of the RCTs included for the live birth outcome. A moderate grading was given by the submission for the evidence on the primary and secondary end points in two of the trials given that allocation concealment and randomisation were not reported. The evaluation concluded that the included randomised trials have a high risk of bias associated with not being able to blind participants to treatment allocation and the trials not providing sufficient details about missing outcome data. The PSCR argued that the performance bias in the trials presented were low and that all methodological issues were addressed by the respective peer-reviewed journals.

6.11 The PBAC noted that the submission did not discuss the discrepancy between the doses in the included trials — specifically the initial dose of 225 IU for the NCT01687712 trial versus the other included trials that used an initial dose of 150 IU.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Gonal-f vs Bemfola</b>						
NCT01121666	372	R, SB 2 cycles	High	ART	Number oocytes retrieved; clinical pregnancy; ongoing pregnancy; live birth	Yes
NCT01687712	1100	R, SB 3 cycles	High	ART	Number oocytes retrieved; clinical pregnancy; ongoing pregnancy; live birth	Yes
<b>Gonal-f vs Ovaleap</b>						
ISRCTN74772901	299	R, SB 1 cycle	High	ART	Number oocytes retrieved; clinical pregnancy; ongoing pregnancy; live birth	Yes
<b>Gonal-f vs Primapur</b>						
NCT03088137	110	R, SB 1 cycle	High	ART	Number oocytes retrieved; ongoing pregnancy; live birth	No
<b>Gonal-f vs Follitrope</b>						
NCT03506243	451	R, SB 1 cycle	High	ART	Number oocytes retrieved; clinical pregnancy; ongoing pregnancy	No

Source: Compiled during evaluation using data from the Chua et al., 2021 meta-analysis and the trial papers included in the meta-analysis. ART = assisted reproductive technology; R = randomised; SB = single blind

### **Comparative effectiveness**

6.12 Tables 4-6 present the differences in the outcomes of live birth, clinical pregnancy and ongoing pregnancy rates and number of oocytes retrieved reported in the five randomised trials. The PBAC considered that none of the individual trials found a significant effect on clinical pregnancy rate, ongoing pregnancy rate or live birth rate for Gonal-f compared with biosimilar preparations of follitropin alfa in the first or subsequent cycles of treatment.

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**Table 4: Results of clinical pregnancy across the trials: dichotomous data**

Trial ID	Cycle	Gonal-f n/N (%)	Biosimilar preparations n/N (%)	Relative risk (95% CI)	Risk difference
<b>Gonal-f vs Bemfola</b>					
NCT01121666	Cycle 1	55/123 (44.7%)	90/249 (36.1%)	0.81 (0.63, 1.04)	-0.09
	<b>Cycle 2</b>	<b>10/38<sup>(a)</sup> (26.3%)</b>	<b>25/72<sup>(a)</sup> (34.7%)</b>	<b>1.32 (0.71, 2.45)</b>	<b>0.084</b>
NCT01687712	Cycle 1	138/ 551 (25.0%)	114/ 549 (20.8%)	0.83 (0.67, 1.03)	-0.04
	Cycle 2	26/120 (21.7%)	17/109 (15.6%)	0.72 (0.41, 1.25)	-0.06
	Cycle 3	0/24 (0%)	5/28 (17.9%)	9.48 (0.55, 163)	0.18
<b>Gonal-f vs Ovaleap</b>					
ISRCTN74772901	Cycle 1	52/146 (35.6%)	43/153 (28.1%)	0.79 (0.56, 1.10)	-0.07
<b>Gonal-f vs Primapur</b>					
NCT03088137	Cycle 1	NR	NR	NR	NR
<b>Gonal-f vs Follitrope</b>					
NCT03506243	Cycle 1	41/112 (36.6%)	103/339 (30.4%)	0.83 (0.62, 1.11)	-0.06

Source: compiled during evaluation using supplementary Table 4 of Chua et al. 2021 meta-analysis and the five RCT papers

CI = confidence interval; NR = not reported

<sup>(a)</sup> per protocol sample sizes were used, corrected in ESC advice.

**Table 5: Results of ongoing pregnancy across the trials: dichotomous data**

Trial ID	Cycle	Gonal-f n/N (%)	Biosimilar preparations n/N (%)	Relative risk (95% CI)	Risk difference
<b>Gonal-f vs Bemfola</b>					
NCT01121666	Cycle 1	55/123 (44.7%)	90/249 (36.1%)	0.81 (0.63, 1.04)	-0.09
	<b>Cycle 2</b>	<b>9/38<sup>(a)</sup> (26.3%)</b>	<b>22/72<sup>(a)</sup> (30.6%)</b>	<b>1.29 (0.66, 2.52)</b>	<b>0.069</b>
NCT01687712	Cycle 1	NR	NR	NR	NR
<b>Gonal-f vs Ovaleap</b>					
ISRCTN74772901	Cycle 1	49/146 (33.6%)	42/153 (27.5%)	0.82 (0.58, 1.15)	-0.06
<b>Gonal-f vs Primapur</b>					
NCT03088137	Cycle 1	16/55 (29.1%)	13/55 (23.6%)	0.81 (0.43, 1.52)	-0.05
<b>Gonal-f vs Follitrope</b>					
NCT03506243	Cycle 1	34/112 (30.4%)	82/339 (24.2%)	0.80 (0.57, 1.12)	-0.06

Source: compiled during evaluation using supplementary Table 4 of Chua et al. 2021 meta-analysis and the five RCT papers

CI = confidence interval; NR = not reported

<sup>(a)</sup> per protocol sample sizes were used, corrected in ESC advice.

**Table 6: Live birth across the trials: dichotomous data**

Trial ID	Cycle	Gonal-f n/N (%)	Biosimilar preparations n/N (%)	Relative risk (95% CI)	Risk difference
<b>Gonal-f vs Bemfola</b>					
NCT01121666	Cycle 1	50/123 (40.7%)	80/249 (32.1%)	0.79 (0.60, 1.05)	-0.09
	<b>Cycle 2</b>	<b>9/38<sup>(a)</sup> (23.7%)</b>	<b>22/72<sup>(a)</sup> (30.6%)</b>	<b>1.29 (0.66, 2.52)</b>	<b>0.069</b>
NCT01687712	Cycle 1	122/551 (22.1%)	101/549 (18.4%)	0.83 (0.66, 1.05)	-0.04
	Cycle 2	25/120 (20.8%)	16/109 (14.7%)	0.70 (0.40, 1.25)	-6.1
	Cycle 3	0/24 (0.0%)	4/28 (14.3%)	6.81 (0.38, 121)	0.14
<b>Gonal-f vs Ovaleap</b>					
ISRCTN74772901	Cycle 1	47/146 (32.2%)	41/153 (26.8%)	0.83 (0.58, 1.18)	-0.05
<b>Gonal-f vs Primapur</b>					
NCT03088137	Cycle 1	12/55 (21.8%)	13/55 (23.6%)	1.08 (0.54, 2.16)	0.02
<b>Gonal-f vs Follitrope</b>					
NCT03506243	Cycle 1	NR	NR	NR	NR

Source: compiled during evaluation using supplementary Table 4 of Chua et al. 2021 meta-analysis and the five RCT papers

CI = confidence interval; NR = not reported

<sup>(a)</sup> per protocol sample sizes were used, corrected in ESC advice.

6.13 Table 7 presents the number of oocytes retrieved by cycle across the trials. This outcome was not reported in the submission but was reported in the Chua et al. (2021) meta-analysis. The PBAC noted that one randomised trial found a significantly greater number of oocytes retrieved in the first cycle of treatment for the biosimilar comparator (Follitrope) compared with Gonal-f, and that otherwise, there was no clinically relevant difference found in number of oocytes retrieved for Gonal-f versus the biosimilar comparators of follitropin alfa for either the first or subsequent cycles of treatment.

**Table 7: Results of number of oocytes retrieved across the trials: continuous data**

Trial ID	Cycle	Gonal-f, mean (SD)	Biosimilar preparations, mean (SD)	Mean difference (Biosimilar preparations Gonal-f), 95% CI
<b>Gonal-f vs Bemfola</b>				
NCT01121666	Cycle 1	10.4 (6.14)	10.7 (5.62)	0.30 (-1.00, 1.60)
	Cycle 2	10.1 (5.3)	10.4 (4.2)	0.30 (-1.12, 1.72)
NCT03088137	Cycle 1	11.62 (6.29)	12.16 (7.28)	0.54 (-2.06, 3.14)
<b>Gonal-f vs Ovaleap</b>				
ISRCTN74772901	Cycle 1	11.9 (6.9)	12.2 (6.8)	0.30 (-1.12, 1.87)
<b>Gonal-f vs Follitrope</b>				
NCT03506243	Cycle 1	<b>12.8 (0.9)</b>	<b>14.9 (0.5)</b>	<b>2.10 (1.92, 2.28)</b>

Source: Compiled during evaluation using supplementary Table 4 of Chua et al. 2021 meta-analysis and the five RCT papers.

CI = confidence interval; RCT = randomised controlled trial; SD = standard deviation

6.14 When comparing biosimilar preparations to Gonal-f for cycle 1 of treatment, the PBAC noted a higher clinical pregnancy rate, ongoing pregnancy rate and live birth rate. However, the PBAC considered that these results were difficult to interpret because the live birth rate could be subject to post-randomisation confounding due to other IVF processes such as the skill of the embryologists and the selection of which embryos to transfer. Additionally, the treatment-centre interactions could affect the livebirth endpoint.

- 6.15 The submission presented additional meta-analyses comparing Gonal-f to biosimilar preparations that are marketed in Australia (i.e., excluding Primapur and Follitrope) for the first cycle of treatment. Gonal-f had a significantly greater clinical pregnancy rate (0.82; 95% CI 0.70, 0.95) and live birth rate (0.82; 95% CI 0.70, 0.96) compared with the biosimilar preparations marketed in Australia.
- 6.16 Additional meta-analysis conducted as part of the evaluation found a higher number of oocytes retrieved in the first cycle of treatment for the biosimilars overall compared with Gonal-f; however, this was driven by the statistically significant results of a single trial of Gonal-f versus Follitrope. The PBAC noted that post-randomisation confounding was not considered in the individual trials because they all pre-specified number-of-oocytes as the primary endpoint as per regulatory guidelines.

### Comparative harms

- 6.17 Table 8 presents a comparison of the key adverse outcome of treatment with follitropin alfa, ovarian hyperstimulation syndrome. The included trials found no significant difference between Gonal-f and biosimilar preparations of follitropin alfa.

**Table 8: Summary of key adverse events in the trials**

Trial ID	Gonal-f n/N (%)	Follitropin alfa biosimilar preparations n/N (%)	RR (95% CI)
<b>Gonal-f vs Bemfola (NCT01121666)</b>			
Ovarian hyperstimulation syndrome	6/123 (4.88)	24/ 249 (9.64)	1.98 (0.83, 4.71)
<b>Gonal-f vs Ovaleap (ISRCTN74772901)</b>			
Ovarian hyperstimulation syndrome	4/146 (2.7)	7/153 (4.6)	1.67 (0.50, 5.59)
Ectopic pregnancy	1/146 (0.7)	2/153 (1.3)	1.91 (0.17, 20.82)
Antepartum haemorrhage	1/146 (0.7)	1/153 (1.3)	0.95 (0.06, 15.12)
<b>Gonal-f vs Bemfola (NCT01687712)</b>			
Ovarian hyperstimulation syndrome (cycle 1)	8/551 (1.45)	7/549 (1.28)	0.88 (0.32, 2.41)
Ovarian hyperstimulation syndrome (cycle 2)	2/120 (1.67)	0/109 (0.00)	0.22 (0.01, 4.53)
Ovarian hyperstimulation syndrome (cycle 3)	0/24 (0.00)	0/ 28 (0.00)	0.86 (0.02, 41.88)
Ectopic pregnancy	1/551 (0.18)	2/549 (0.36)	2.01 (0.18, 22.07)
Spontaneous miscarriage	5/551 (0.91)	2/549 (0.36)	0.40 (0.08, 2.06)
<b>Gonal-f vs Primapur (NCT03088137)</b>			
Ovarian hyperstimulation syndrome	2/ 55 (3.64)	0/ 55 (0.00)	0.20 (0.01, 4.07)
Spontaneous miscarriage	2/55 (3.64)	0/55(0.00)	0.20 (0.01, 4.07)
<b>Gonal-f vs Follitrope (NCT03506243)</b>			
Ovarian hyperstimulation syndrome	5/112 (4.46)	4/ 339 (1.18)	0.26 (0.07, 0.97)

Source: Compiled during evaluation using supplementary Table 4 of Chua et al. 2021 meta-analysis and the five RCT papers  
 CI = confidence interval; RCT = randomised controlled trial; RD = risk difference; RR = relative risk

**Benefits/harms****Table 9: Summary of comparative benefits and harms for Gonal-f and biosimilar preparations of follitropin alfa**

Trial	Gonal-f n/N	Biosimilar preparations n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Gonal-f n/N (%)	Biosimilar preparations n/N (%)	
<b>Benefits</b>						
<b>Live birth rate (after 1 cycle)</b>						
NCT01121666	50/123	80/249	0.79 (0.60, 1.05)	40.7	32.1	-0.09 (-0.19, 0.02)
NCT01687712	122/551	101/549	0.83 (0.66, 1.05)	22.1	18.4	-0.04 (-0.08, 0.01)
ISRCTN74772 901	47/146	41/153	0.83 (0.58, 1.18)	32.2	26.8	-0.05 (-0.16, 0.05)
NCT03088137	12/55	13/55	1.08 (0.54, 2.16)	21.8	23.6	0.00 (-0.15, 0.15)
Meta-analysis	231/875	234/1006	0.83 (0.71, 0.97)	26.4	23.3	-0.05 (-0.09, -0.01)
<b>Ongoing pregnancy rate (after 1 cycle)</b>						
NCT01121666	55/123	90/249	0.81 (0.63, 1.04)	44.7	36.1	-0.09 (-0.19, 0.02)
ISRCTN74772 901	49/146	42/153	0.82 (0.58, 1.15)	33.6	27.5	-0.06 (-0.17, 0.04)
NCT03088137	16/55	13/55	0.81 (0.43, 1.52)	29.1	23.6	0.05 (-0.11, 0.22)
NCT03506243	34/112	82/339	0.80 (0.57, 1.12)	30.4	24.2	0.06 (-0.03, 0.16)
Meta-analysis	154/436	227/796	0.81 (0.68, 0.96)	26.2	24.8	-0.07 (-0.12, -0.01)
<b>Clinical pregnancy rate (after 1 cycle)</b>						
NCT01121666	55/123	90/249	0.81 (0.62, 1.04)	44.7	36.1	-0.09 (-0.19, 0.02)
NCT01687712	138/ 551	114/549	0.83 (0.67, 1.03)	25.0	20.8	-0.04 (-0.09, 0.01)
ISRCTN74772 901	52/146	43/153	0.79 (0.56, 1.10)	35.6	28.1	-0.08 (-0.18, 0.03)
NCT03506243	41/112	103/339	0.83 (0.62, 1.11)	36.6	30.4	-0.06 (-0.16, 0.04)
Meta-analysis	286/932	350/1290	0.82 (0.72, 0.94)	30.8	27.3	-0.06 (-0.10, -0.02)
<b>Harms</b>						
	Gonal-f n/N	Biosimilar preparations n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Gonal-f	Biosimilar preparations	
<b>Ovarian hyperstimulation syndrome (after cycle 1)</b>						
NCT01121666	6/123	24/ 249	1.98 (0.83, 4.71)	4.9	9.6	0.05 (-0.01, 0.10)
NCT01687712	8/551	7/549	0.88 (0.32, 2.41)	1.5	1.3	-0.00 (-0.02, 0.01)
ISRCTN74772 901	2/146	4/153	1.91 (0.35, 10.26)	1.4	2.6	0.01 (-0.02, 0.04)
<b>Ectopic pregnancy</b>						
NCT01687712	1/551	2/549	2.01 (0.18, 22.07)	0.2	0.4	0.00 (-0.00, 0.01)
ISRCTN74772 901	1/146	2/153	1.91 (0.17, 20.82)	0.7	1.3	0.01 (-0.02, 0.03)

Source: Compiled during evaluation using supplementary Table 4 of Chua et al. 2021 meta-analysis and the five RCT papers  
HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio

6.18 Based on direct evidence presented by the submission, for every 100 patients treated with Gonal-f in comparison with Bemfola for cycle 1 of treatment:

- Approximately 3.0 additional patients would have clinical pregnancies.
- Approximately 2.6 additional patients would have ongoing pregnancies.
- Approximately 2.8 additional patients would have live births.

- The evaluation calculated no significant difference in the number of oocytes retrieved.

### **Clinical claim**

- 6.19 The submission described Gonal-f as superior in terms of effectiveness for fertility treatment compared with biosimilar preparations of follitropin alfa, and non-inferior in terms of safety compared to the biosimilars. More specifically, the submission stated that Gonal-f resulted in significantly greater rates of clinical pregnancy, ongoing pregnancy and live birth compared with the biosimilar preparations of follitropin alfa. The submission described Gonal-f as non-inferior in terms of safety compared to the biosimilar preparations of follitropin alfa.
- 6.20 The PBAC considered that the therapeutic conclusion presented in the submission was not supported because the submission did not present the necessary information on the in-vitro characterisation of the biosimilars in their submission. Although the PSCR noted that the evidence provided in the submission was considered acceptable to support the registration of follitropin alfa biosimilars internationally, as noted in paragraph 3.3 above, the PBAC considered that even if the Chua et al. (2021) meta-analysis was supportive of the submission's clinical claim, it would not be appropriate to consider in isolation the randomised clinical endpoint trials such as those in the Chua et al. (2021) meta-analysis.
- 6.21 The PBAC noted other key issues including:
- The findings of the systematic review might be subject to publication bias that may favour Gonal-f compared with the biosimilar comparators (as acknowledged by Chua et al. (2021)).
  - the validity of the meta-analysis was unclear because:
    - possibility of post-randomisation confounding with the endpoint of livebirths was not considered
    - related to the above point, treatment-centre interactions could affect the livebirth endpoint and should be considered
    - all clinical endpoint studies, including non-randomised studies, should have been identified and considered for inclusion in the meta-analysis. Even if these studies could not be combined in a meta-analysis, the results of any non-randomised studies would be informative
    - statistical multiplicity should be considered and discussed by the sponsor given live births was a secondary endpoint in all the individual trials included in the meta-analysis; whereas number-of-oocytes was the primary endpoint in the individual trials and showed non-inferiority in the meta-analysis.

- 6.22 The PBAC considered that the claim of the superior comparative effectiveness of Gonal-f was not adequately supported by the data.
- 6.23 The PBAC considered that the claim of non-inferior comparative safety was reasonably supported by the data.

**Economic analysis**

- 6.24 The type of economic evaluation presented was a cost-effectiveness analysis, of Gonal-f versus the biosimilars for ovarian stimulation. Bemfola was used as a proxy for all the biosimilars. The evaluation considered that the use of Bemfola solely as the proxy for all biosimilars might not be appropriate. The submission first argued that Gonal-f is therapeutically distinct from other follitropin alfa biosimilars, then assumed, without providing justification, that all biosimilars (other than Gonal-f) are clinically interchangeable.
- 6.25 The PBAC considered that the submission’s clinical evidence did not support the cost-effectiveness analysis, because there was insufficient evidence to conclude that Gonal-f is superior in terms of comparative effectiveness to biosimilar preparations of follitropin-alfa.
- 6.26 The submission presented a stepped economic evaluation; the steps are summarised in Table 10. Table 11 provides key components of the economic evaluation.

**Table 10: Steps in the economic evaluation**

Step	Description
Step 1	One-cycle, trial-based. Cost = MBS and PBS costs for an IVF cycle Outcome = incremental cost per additional clinical pregnancy
Step 2	One-cycle, trial-based. Cost = MBS and PBS costs for an IVF cycle + costs of miscarriage Outcome = incremental cost per additional live birth
Step 3	Multiple cycle (maximum of 8 cycles), model-based Cost = MBS and PBS costs for an IVF cycle + costs of miscarriage Outcome = incremental cost per additional live birth

Source: Table 6, p32 of the submission.

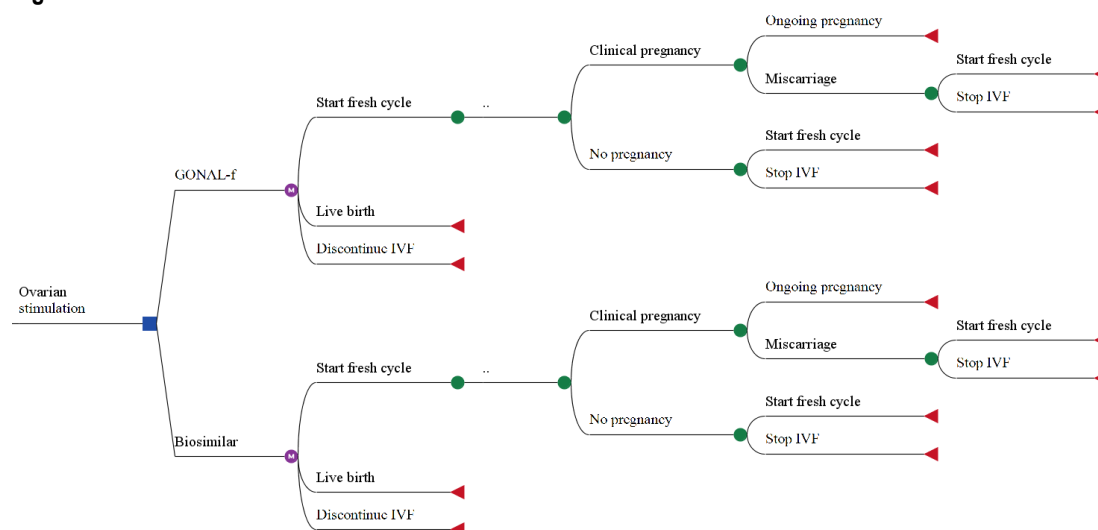
**Table 11: Summary of model structure, key inputs, and rationale**

Component	Summary
Treatments	Gonal-f vs Bemfola (as a proxy for all biosimilar preparations of follitropin alfa)
Time horizon	Steps 1 and 2: one IVF cycle Step 3: multiple IVF cycles, maximum of 8
Outcomes	Step 1: clinical pregnancy Steps 2 and 3: live births
Methods used to generate results	Markov cohort
Health states	Start fresh cycle, live birth, discontinue IVF
Cycle length	Unspecified and variable (as one IVF cycle)
Transition probabilities or Allocation to health states (if partitioned survival model)	Probability of clinical pregnancy, Probability of live birth from pregnancy, Probability of miscarriage Probability of starting a fresh IVF cycle
Extrapolation method	Constant risk ratio of clinical pregnancy rate for 8 cycles Probability of clinical pregnancy = risk ratio * cycle-specific delivery rates (UNSW ART in ANZ 2018)

Source: Compiled during the evaluation using pp34-51 of the submission

6.27 The economic model presented in the submission was a Markov cohort, with two arms (Gonal-f vs Biosimilar), each of which had three states: (1) New IVF cycle, from which an individual could either achieve clinical pregnancy, leading to either a live birth or miscarriage that results in starting a fresh cycle, stopping IVF, or failing to have a pregnancy that leads to either start a fresh cycle or stop IVF, (2) Live birth (terminal/absorbing state) and (3) Discontinue IVF (terminal/absorbing state).

**Figure 1: Model structure**



Source: Figure 12, p37 of the submission.

6.28 The submission did not provide adequate detail of the population in the model other than stating “the population receiving Gonal-f in Australian clinical practice”. The model did not account for any potential differences in age at the first IVF cycle with respect to clinical pregnancy rates, probabilities of having a live birth, and restarting IVF cycles following a miscarriage. The evaluation stated that this hindered the assessment of the extent to which the modelled population reflects the target

Australian population. The PBAC considered that there are important differences between the population included in most of the clinical trials and the population used in the economic model. As discussed in paragraph 6.7, the effectiveness of Gonal-f for the Australian population may be lower than what was observed in the trials based on the difference in age between the Australian population and the trials.

- 6.29 The time horizon was not specified in the economic model. Instead, the model was based on IVF cycles. The PBAC considered this appropriate. Steps 1 and 2 of the economic evaluation consisted of one IVF cycle and step 3 – the base-case model – consisted of a maximum of 8 cycles.
- 6.30 The submission rationalised using a maximum of 8 cycles while other models in the literature used a maximum of 2-3 cycles, because an unlimited number of cycles is funded in Australia. The University of New South Wales ART in Australia and New Zealand (UNSW ART in ANZ) report (2018) reported live birth rates from up to 10 cycles, and the submission's input data was also prepared for a model with a maximum of 10 cycles. From the submission's base-case model with an 8-cycle maximum, the average number of cycles estimated for the Gonal-f arm was 2.39 and for the Biosimilar was 2.57. If the maximum number of IVF cycles was 10, the average number of cycles would be 2.42 and 2.61 for the Gonal-f and biosimilar arms, respectively. The evaluation noted that these estimates are closer to the value reported in the UNSW ART in ANZ report (2018) (2.61 cycles). The PBAC agreed with the evaluation and considered that the rationale for a maximum of 8 IVF cycles was not well supported.
- 6.31 The model assumed a constant risk ratio for all cycles. The PBAC considered this was inappropriate as it did not reflect the different treatment efficacy from cycle 2 onwards.
- 6.32 The model estimated that patients in the Gonal-f arm, on average, received 2.39 IVF cycles while patients in the biosimilar arm received 2.56 IVF cycles. The submission then stated that these estimates are closely aligned with the Australian and New Zealand Assisted Reproduction Database (ANZARD) 2018 report, therefore the economic model was validated. The evaluation considered that it is inappropriate to validate the modelled estimates of live birth rates and average numbers of IVF cycles with the same source used to derive the transition probabilities behind the modelled estimates.
- 6.33 The submission included PBS and MBS costs associated with the products (Gonal-f and Bemfola, as the proxy for all biosimilars) and IVF cycles, including the cost of miscarriage. However, the cost of delivery (including potential complications) was omitted.
- 6.34 The key outcome of step 1 was the cost per clinical pregnancy, and that of steps 2 and 3 was the cost per live birth. The results presented in the submission are shown in Table 12. The submission concluded that Gonal-f, at the proposed price, is cost effective with an ICER of \$0 to < \$5,000 per live birth, compared to the biosimilar

preparations of follitropin alfa (proxied by Bemfola). The PBAC considered that the ICER is highly uncertain and likely to favour Gonal-f.

**Table 12: Results of the stepped economic evaluation**

Step and component	Proposed medicine (Gonal-f)	Comparator (Bemfola)	Increment
<b>Step 1: trial-based evaluation (cost/clinical pregnancy)</b>			
Costs (\$)	█	\$5,775	█
Clinical pregnancy	0.2988	0.245	0.05
Incremental cost/extra clinical pregnancy			█ <sup>1</sup>
<b>Step 2: trial-based evaluation (cost/live birth)</b>			
Costs (\$)	█	\$5925	█
Live birth	0.23	0.19	0.04
Incremental cost/extra live birth			█ <sup>1</sup>
<b>Step 3: base-case modelled (up to eight IVF cycles)</b>			
Costs (\$)	█	\$15,171	█
Live birth	0.53	0.46	0.07
Incremental cost/ live birth			█ <sup>2</sup>

Source: Tables 15, 16, and 17, pp47-48 of the submission

The redacted values correspond to the following ranges:

<sup>1</sup> \$5,000 to < \$15,000

<sup>2</sup> \$0 to < \$5,000

- 6.35 The submission presented five one-way sensitivity analyses, two of which reflect the ICER changes with respect to the key driver of the model – the risk ratio of clinical pregnancy rates between Gonal-f and Bemfola. However, the submission did not consider the key assumption of constant risk ratio between Gonal-f and Bemfola. Only cycle 1’s risk ratio was used in the model and was assumed to be constant for all 8 cycles. An additional meta-analysis conducted during the evaluation showed that the risk ratio of cycle 2 substantially differed from that of cycle 1. Thus, the evaluation considered that the constant risk ratio assumption was not adequately supported. The PSCR acknowledged the use of a constant risk ratio potentially overestimates the long-term benefit, and presented a revised base-case for the model in which the incremental treatment effect for clinical pregnancy diminishes over time until cycle 3 and assumes no incremental benefit from cycle 4 onwards. This increased the base case ICER of \$0 to < \$5,000 per live birth (clinical pregnancy RR of 0.82 used in all cycles) to \$5,000 to < \$15,000 per live birth.
- 6.36 During the evaluation, additional sensitivity analyses were conducted, and the additional analyses confirmed that the cost effectiveness results were highly sensitive to the estimated risk ratio of clinical pregnancy rate between Bemfola and Gonal-f. This risk ratio was calculated for the clinical pregnancy rate in cycle 1 for biosimilar versus Gonal-f, and the PBAC considered that this was not applicable to the other IVF cycles.

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Table 13: Results of sensitivity analyses

Analyses	Incremental cost (\$)	Incremental live birth	ICER
Base case, 8 IVF cycle	█	0.07	█ <sup>1</sup>
<b>Sensitivity analyses presented in the submission</b>			
Chua et al 2021 lower 95% CI around clinical pregnancy rate = 0.7 (base case = 0.82)	Not reported	Not reported	Dominates
Chua et al 2021 upper 95% CI around clinical pregnancy rate = 0.95 (base case = 0.82)	Not reported	Not reported	█ <sup>2</sup>
Discontinuation rate increases in subsequent cycles (by 1% per cycle)	Not reported	Not reported	█ <sup>1</sup>
Clinical pregnancy rate does not diminish in subsequent cycles	Not reported	Not reported	█ <sup>1</sup>
89% of patients with clinical pregnancy achieve live birth (Chua et al. (2021))	Not reported	Not reported	Dominates
All strengths of Bemfola are used (accept the 75 IU)	Not reported	Not reported	Dominates
<b>Additional sensitivity analyses during the evaluation</b>			
Risk ratio of 0.82 for cycle 1, subsequent cycles have constant risk ratio of 1 (no differences between Gonal-f and biosimilar clinical pregnancy rate in cycles 2+)	█	0.0457	█ <sup>3</sup>
Upper 95% CI around the risk ratio of clinical pregnancy rate of Bemfola (only) versus Gonal-f = 0.97 (base case = 0.82)	█	0.0104	█ <sup>4</sup>

Source: Table 18, p51 of the submission, and conducted during the evaluation

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$5,000

<sup>2</sup> \$35,000 to < \$45,000

<sup>3</sup> \$5,000 to < \$15,000

<sup>4</sup> \$75,000 to < \$95,000

Table 14: Key drivers of the model

Description	Method/Value	Impact Base case: \$ [redacted] <sup>1</sup> per live birth
Extrapolation	Risk ratio of 0.82 clinical pregnancy rates for Gonal-f versus biosimilars in cycle 1 was used for all 8 cycles	<p>High</p> <p>A small change in the risk ratio led to a very large change in the ICER estimates because a higher chance of clinical pregnancy resulted to higher ongoing pregnancy and live birth rates (while the miscarriage and IVF discontinuation rates rated were identical for both treatment arms).</p> <p>The constant risk ratio favouring Gonal-f was applied for all eight cycles, leading to the compounded effect of effectiveness</p> <p>The PSCR presented a revised base-case for the model where the incremental treatment effect for clinical pregnancy diminishes over time until cycle 3 and assumes no incremental benefit from cycle 4 onwards:                      Risk ratio cycle 1 = 0.82                      Risk ratio cycle 2 = 0.93                      Risk ratio cycle 3 = 0.965 (midpoint between 0.93 and 1)                      Risk ratio cycle 4+ = 1 (constant and equal for both) treatment arms)</p> <p>This increased the ICER to \$ [redacted] <sup>2</sup> per live birth.</p>

Source: Additional sensitivity analyses during the evaluation.

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$5,000

<sup>2</sup> \$5,000 to < \$15,000

### Estimated PBS usage & financial implications

6.37 This submission was not considered by the DUSC.

6.38 The submission applied a market share approach (based on the number of IVF cycles) to estimate the impact of Gonal-f use on the PBS and MBS budget. Gonal-f is a direct substitution of the currently listed recombinant human follicle stimulating hormone (r-hFSH) therapy (Bemfola), thus the current Bemfola market share was used in the analysis.

6.39 Four main data sources were used in the financial estimation:

- the MBS data for the total number of IVF cycles and the services used for IVF
- the PBS data for all the products required for IVF treatment (including Gonal-f and Bemfola)
- the UNSW ART in ANZ 2018 report for the transition probability calculation
- and the economic model for the estimated average number of IVF cycles for each treatment arm

Detailed evaluation of each input is shown in Table 15.

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Table 15: Data sources applied in the utilisation and financial estimates

Data	Source	Comment
Total number of IVF cycles (whole market for follitropin alfa and beta)	Projection from MBS data: estimated growth rate of 2.3% per annum, from historical data (actual IVF cycles 2015 – 2020). Estimated numbers were not presented in the submission but in the Section 4 Workbook.	Highly uncertain.  The historical data implied a much higher growth rate with wide fluctuations. Between 2018-2020, the growth rate was progressively higher, from 3.4% to 7.4% and 9%, respectively. The prior period consisted of both negative and positive growth.  It might be more appropriate to use the PBS market data for the projection because the PBS data would have accounted for wastage.
% Use of follitropin alfa per IVF cycle	Calculated from PBS data May 2020 to April 2021: market share of follitropin alfa (Bemfola + Gonal-f) use for IVF.  Gonal-f accounted for 47.3% and Bemfola 13.2% (total 60.6%) of all IVF MBS items.	The assumption is reasonable.  The submission stated that the market share of follitropin alfa is expected to rise to ■% in 2027 (Yr 6). However, the calculation in the excel spreadsheet was based on a constant ■% from 2022-2027. Therefore, the estimated numbers presented in the submission differed from the numbers calculated in the Section 4 Workbook.
% Gonal-f within follitropin alfa market, <b>without</b> Chua et al 2021	No source cited in the submission (information not shown in the submission, but in the Section 4 Workbook).	An insufficient PBS time series was presented in the submission to verify the claim of downward trending (status quo). An independent analysis (during the evaluation) of the PBS scripts by months (May 2020 – April 2021) showed that the Gonal-f market share fluctuated, mostly around 78%-80% without a clear downward trend.
% Gonal-f within follitropin alfa market, <b>with</b> Chua et al 2021	Assumption: Gonal-f had better live birth outcomes compared to biosimilar.  The submissions stated that the clinical results from Chua et al (2021) would reduce biosimilar usage by ~1% per year and increase Gonal-f's market share by ~1% (i.e. offset each other 1:1).	Uncertain.  The clinical evidence presented in the submission was not sufficient to conclude that Gonal-f had better live birth outcomes, across all cycles, compared to the biosimilars.
Change of Gonal-f units dispensed	Calculated.  Total number of IVF cycles * % use of follitropin alfa per IVF cycles * (% Gonal-f share with Chua et al 2021 - % Gonal-f share without Chua et al 2021).	The increase in Gonal-f scripts was completely offset by the reduction in Bemfola scripts.  The estimated number presented in the submission was not consistent with the Section 4 Workbook. The differences, however, are small.  This calculation is not consistent with the assumption that the submission used to calculate the number of IVF cycles reduced if Gonal-f is used, due to better live birth outcomes (see below).

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Data	Source	Comment
Number of IVF cycles avoidable per patient	<p>Avoided cycle per patient was estimated from the economic model in Section 3 (based on Chua et al 2021 risk ratio of live birth outcome for cycle 1 of Gonal-f versus biosimilars).</p> <p>Average IVF cycles per patient in the Gonal-f arm: 2.388</p> <p>Average IVF cycles per patient in the Bemfolia arm: 2.566</p> <p>Avoid IVF cycles per patient in the Gonal-f arm = <math>2.566 - 2.388 = 0.176</math></p>	<p>The submission stated that Chua et al 2021 found that Gonal-f results in better live birth outcomes, therefore, the use of Gonal-f would lead to a reduction in the average IVF cycles per patient, compared to the biosimilars (Section 3, economic evidence). The application of the Chua et al results were not appropriate as the average number of cycle differences were entirely driven by the risk ratio of Gonal-f versus biosimilars in cycle 1 and extrapolated to 8 cycles.</p> <p>Additionally, the calculation of “avoidable” cycle per patient should they switch from a biosimilar to Gonal-f was used solely for the MBS calculation, and not accounted for in the script calculation. If switching to Gonal-f reduced the number of total IVF cycles, then both PBS scripts of Gonal-f and MBS services used for IVF cycles would be affected.</p>
Scripts dispensed	Assumption: one script per IVF cycle, therefore the number of IVF cycles for each product = the number of scripts for the respective product.	<p>Uncertain.</p> <p>The assumption of a 1:1 ratio of IVF cycle: script did not account for wastage. However, the wastage might be small.</p>
Proposed medicine	<p>Requested price; PBS item number: 6433N</p> <p>The requested price (\$██████) is the reverse of the 16% reduction of price introduced when biosimilars entered the market. Current DMPQ = \$1,685.14</p>	Reasonable.
Comparator	PBS item number: 10866X	Reasonable.
Patient co-payment	PBS statistics: percentage of patients by beneficiary split.	Reasonable.
MBS costs	<p>MBS items 13201, 13202, 13203, 13209, 13212, 13215, 13251</p> <p>% of patients associated with each MBS item.</p> <p>The average MBS costs per IVF cycle = the sum product of the MBS item costs, and the % of patients associated with the MBS items.</p>	Reasonable, however the submission did not apply the 85% reimbursement, but instead applied 100% to calculate the cost offsets.

Source: compiled during the evaluation

6.40 The submission estimated:

- An increase in the use of Gonal-f scripts, driven by both the IVF market growth and patients choosing Gonal-f over other biosimilars; and the associated fall in biosimilar scripts. The submission did not account for a reduction in the number of Gonal-f scripts used due to the avoided IVF cycles in patients who used Gonal-f, which was used to calculate the MBS savings.
- An increase in the PBS net cost of Gonal-f, driven by both more Gonal-f script use and a higher (proposed) price. The submission underestimated the PBS net

cost (by about \$30M < \$40M over the six-year period) due to a calculation error, where the incorrect number of scripts was used to calculate the total PBS cost for Gonal-f.

- MBS savings induced by avoided IVF cycles in patients who use Gonal-f, based on the estimated difference in the average number of IVF cycles per patient between Gonal-f and biosimilar from the economic model. The difference in the average number of IVF cycles of the two treatment arms was driven entirely by the risk ratio of clinical pregnancy rates in cycle 1 (in favour of Gonal-f), which was not well supported by the clinical data. This difference, and thus the avoided IVF cycles in patients using Gonal-f, is highly uncertain and unlikely to be realised. The estimated MBS savings are therefore unreasonable. Additionally, the submission used the full MBS costs for each of the service items instead of the 85% rate.
- A PBS/MBS net cost of approximately \$0 to < \$10M to the government in listing Gonal-f with the proposed price (DPMQ = \$ [REDACTED]) over the six-year period (2022-2027). This net cost was heavily underestimated. After correcting all errors made in the submission while keeping the presented assumptions (including the MBS savings), the PBS/MBS net cost was calculated by the evaluation to be \$40M to < \$50M over the six-year period.

6.41 The estimated use and financial implications are summarized in Table 16 below. Only corrected estimates are shown.

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Table 16: Estimated use and financial implications (estimates with correct formula and numbers, or numbers from the excel file – rather than from the submission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Status quo scenario (no changes)</b>						
Number of Bemfola units dispensed per year (without Chua et al 2021)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Number of Gonalf units dispensed per year (without Chua et al 2021)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Total PBS cost of Bemfola, net co-payment	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
Total PBS cost of Gonalf, net co-payment	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>6</sup>
Total PBS cost of Gonalf and Bemfola (net co-payment)	█ <sup>6</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>
<b>Proposed scenario (revised DPMQ for Gonalf, impact of Chua et al 2021 on utilisation)</b>						
Number of Bemfola units dispensed per year (with Chua et al 2021)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Number of Gonalf units dispensed per year (without Chua et al 2021)	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Total PBS cost of Bemfola, net co-payment	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>8</sup>	█ <sup>4</sup>
Total PBS cost of Gonalf, net co-payment	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>9</sup>	█ <sup>9</sup>
Total PBS cost of Gonalf and Bemfola (net co-payment)	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>10</sup>
Avoided IVF cycles	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>

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	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Implied MBS savings due to avoid IVF cycles (with 85%)	██████████ <sup>8</sup>	██████████ <sup>8</sup>	██████████ <sup>8</sup>	██████████ <sup>8</sup>	██████████ <sup>8</sup>	██████████ <sup>8</sup>
<b>Net financial implications</b>						
Overall net cost to the PBS, taking into account Gonal-f replacement of biosimilars	██████████ <sup>4</sup>	██████████ <sup>4</sup>	██████████ <sup>4</sup>	██████████ <sup>4</sup>	██████████ <sup>4</sup>	██████████ <sup>4</sup>
Overall net cost to the PBS and MBS	██████████ <sup>8</sup>	██████████ <sup>8</sup>	██████████ <sup>8</sup>	██████████ <sup>8</sup>	██████████ <sup>8</sup>	██████████ <sup>8</sup>

Source: Tables from the submission and the excel file, and calculation during the evaluation.

The redacted values correspond to the following ranges:

- <sup>1</sup> 5,000 to 10,000
- <sup>2</sup> 20,000 to < 30,000
- <sup>3</sup> 30,000 to < 40,000
- <sup>4</sup> \$10 million to < \$20 million
- <sup>5</sup> \$40 million to < \$50 million
- <sup>6</sup> \$50 million to < \$60 million
- <sup>7</sup> \$60 million to < \$70 million
- <sup>8</sup> \$0 to < \$10 million
- <sup>9</sup> \$70 million to < \$80 million
- <sup>10</sup> \$80 million to < \$90 million
- <sup>11</sup> 500 to < 5,000

6.42 Apart from errors in the calculation and inconsistencies between the estimates presented in the submission and the Section 4 Workbook, the main issues identified with the estimates are:

- The submission calculated the avoided cycles by Gonal-f to estimate the MBS impact, but did not incorporate these savings into the calculation of total number of IVF cycles that would use Gonal-f scripts. This is a logical inconsistency.
- The predicted potential savings are not well supported, and unlikely in practice, because the superior clinical efficacy of Gonal-f versus biosimilar was not well supported, and the number of IVF cycles estimated from Section 3 was driven entirely by the clinical efficacy assumption (risk ratio of clinical pregnancy ratio between Gonal-f and biosimilar preparations of follitropin alfa).
- If the predicted MBS savings were removed and calculation errors were correct, then listing Gonal-f with the proposed price (DPMQ = \$██████████) would result in a net cost of \$80M to < \$90M over the six-year period (2022-2027) to the Government.

6.43 The PSCR presented a revised financial analysis which acknowledged the calculation errors in the submission and included the decreasing benefit in live birth rate over a number of cycles in accordance with the revised economic evaluation. However, the PSCR maintained the MBS savings due to patients switching from biosimilars to GONAL-f, albeit at a lower rate. Under the revised analysis, the financial impact of listing GONAL-f at the requested price would result in the net cost to the PBS of \$50 million to < \$60 million over the six-year period, with MBS savings of \$30M to < \$40M, and therefore a net cost to the Government of \$10 million to < \$20 million. The PBAC considered that the financial impact was uncertain given that the estimates were dependent on the submission's clinical claim that Gonal-f was superior in terms of efficacy compared to the other biosimilars, a claim that the PBAC considered was not adequately supported.

6.44 The PBAC noted that the pre-PBAC response also provided revised financial estimates.

### ***Quality use of medicines***

6.45 The submission discussed quality use of medicines (QUM) issues regarding "a-flagging" and switching between Gonal-f and Ovaleap. The submission noted there would be potential QUM issues associated with switching between biosimilar preparations of follitropin alfa. The submission noted that training on the self-administration of fertility treatment would depend on which biosimilar of follitropin alfa is used. The submission discussed the potential for patient confusion and medication error related to substitution at the pharmacy level.

6.46 At its July 2021 meeting, the PBAC recommended that Gonal-f and Ovaleap should be treated as equivalent to each other for the purposes of substitution (i.e., 'a' flagged in Schedule). The PBAC noted that flow on changes arising from listing Ovaleap would entail the addition of 'a-flags' to the Gonal-f listings to indicate equivalence for the purposes of substitution.

6.47 The PBAC considered a range of other factors in forming its view on 'a' flagging including:

- The results from the international, multi-centre, Phase III, randomised, assessor-blind, comparator controlled, parallel group efficacy and safety trial (XM17-05) of Ovaleap in comparison to Gonal-f and the TGA Delegate's view that Ovaleap is similar to Gonal-f, with comparable pharmacokinetics, efficacy, safety, and immunogenicity.
- Unlike with Bemfola, the manner of administration, strengths, number of units per pack and maximum quantities are the same between Ovaleap and Gonal-f.
- The evidence (Chua et al. 2021) presented by organisations in support against a-flagging had not been evaluated. The safety concerns can be addressed through education.

- Prescribers have the option to specify “No Brand Substitution Permitted” should they have individual concerns about brand substitution. Pharmacists have a responsibility to adhere to these directions where specified.
- 6.48 While the PBAC noted the differences in administration techniques of Ovaleap and Gonal-f, it considered that patients with sufficient education/training resources would be able to administer the different devices appropriately. The PBAC had advised that the sponsor of Ovaleap should work with key bodies to develop education and training resources on how to use Ovaleap. The PBAC reiterated its advice that educational activities should be targeted at all prescribers as well as pharmacists. The PBAC noted that the prescribing clinician would have the option to specify “No Brand Substitution Permitted” should they wish to prescribe a particular brand. The PBAC requested the sponsor and the Department work together with NPS MedicineWise and the Pharmaceutical Society of Australia to ensure pharmacists are educated on the product differences between follitropin alfa devices.
- 6.49 The PBAC had also advised that Ovaleap and Bemfola should not be considered equivalent for the purpose of substitution, noting that Ovaleap shared the same differences with Bemfola as Gonal-f, and that these differences would make substitution at the pharmacy level difficult from a practical perspective.

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend an increase to the price of Gonal-f as it considered that the clinical claim of superior comparative effectiveness of Gonal-f to all of the follitropin alfa biosimilars was not adequately supported by the data presented in the submission. The PBAC also reaffirmed its previous advice that Gonal-f and Ovaleap should be treated as equivalent for the purposes of substitution (i.e. ‘a’ flagged in the Schedule).
- 7.2 The PBAC noted that a claim of superior effectiveness of the reference brand to the biosimilar brand would be contradictory to the decision made by the TGA and other Regulatory Agencies (e.g., EMA) under the biosimilar regulatory framework. The PBAC considered that a totality of evidence approach, including the in-vitro characterisation of the molecule, pharmacokinetic analyses and randomised clinical endpoint trials, would be required to support the submission’s clinical claim.
- 7.3 The PBAC further noted that the clinical endpoint studies were not designed with livebirths as the primary endpoint and consequently interpretation of the result for livebirths is problematic, given the potential for post-randomisation confounding and treatment-centre interactions that were not formally accounted for in the statistical analysis plans of the individual studies (given livebirths was not the pre-specified primary endpoint).
- 7.4 The PBAC noted that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the

committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. The PBAC considered that the evidence provided did not demonstrate that Gonal-f provides a significant improvement in efficacy and/or reduction of toxicity over its biosimilars.

- 7.5 Given that the PBAC considered that the claim of the superior comparative effectiveness of Gonal-f was not adequately supported by the data, the PBAC did not recommend the submission's request that Gonal-f not be marked as equivalent for the purposes of substitution with Ovaleap. The PBAC recalled its July 2021 advice in relation to Ovaleap that, while administration techniques of Ovaleap and Gonal-f differ, patients with sufficient education/training resources would be able to administer the drug appropriately despite different devices. The PBAC noted in its July 2021 consideration of Ovaleap that in practice the prescribing clinician would have the option to specify "No Brand Substitution Permitted" should they have individual concerns about brand substitution. Pharmacists have a responsibility to adhere to these directions where specified.
- 7.6 The PBAC considered that the submission's clinical evidence did not support the cost-effectiveness analysis, because there was insufficient evidence to conclude that Gonal-f is superior in terms of comparative effectiveness to biosimilar preparations of follitropin-alfa. Further, the PBAC considered that the financial estimates were not supported, given that the estimates were dependent on the submission's clinical claim that Gonal-f was superior in terms of efficacy compared to the other biosimilars.
- 7.7 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

The sponsor had no comment.