

**6.18 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,**  
**Ovaleap<sup>®</sup>,**  
**Theramex Australia Pty Ltd**

**1 Purpose of Application**

- 1.1 The Category 3 submission sought Section 85 and Section 100 IVF listing of a new biosimilar medicine, follitropin alfa (Ovaleap<sup>®</sup>) in the form of 300 I.U., 450 I.U. and 900 I.U. under the same conditions as its PBS-listed reference biologic (Gonal-f<sup>®</sup>).

**2 Background**

***Registration status***

- 2.1 Ovaleap was TGA registered on 10 March 2021 for:
- the treatment of anovulatory infertility in women who have been unresponsive to clomiphene citrate or where clomiphene citrate is contraindicated,
  - for controlled ovarian hyperstimulation in women undergoing Assisted Reproductive Technology (ART),
  - and 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 Ovaleap has not been considered by the PBAC previously.
- 2.3 The originator brand of follitropin alfa, Gonal-f, was first considered by the PBAC in December 1997, and first listed on 1 April 1998.
- 2.4 The first follitropin alfa biosimilar product Bemfola<sup>®</sup>, was recommended in March 2016 and listed on 1 August 2016.

**3 Requested listing**

- 3.1 The proposed listings were for all the indications for which the reference brand Gonal-f is currently PBS listed:
- women undergoing Assisted Reproductive Technology (ART),

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- anovulatory infertility,
  - infertility due to hypogonadotropic hypogonadism.
- 3.2 The submission requested the PBAC consider if removing the authority requirement for the S100 IVF listings is appropriate (i.e. changing the listings to restricted benefits). The PBAC did not consider that changing the S100 IVF listings to restricted benefits would have a meaningful impact on uptake. As such, the PBAC did not recommend removing the authority requirement for these listings.
- 3.3 The submission requested listing three existing strengths (300 I.U., 450 I.U. and 900 I.U.) in the form of cartridges (the existing trade products have the forms of 'pen device' and 'pen devices') and for Ovaleap to be considered equivalent ('a'-flagged) with the corresponding 'Gonal-f' branded products for the purposes of substitution, as outlined in the tables below. The PBAC considered this to be appropriate.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<b>FOLLITROPIN ALFA</b>					
<i>follitropin alfa 300 units (22 microgram)/0.5 mL injection, 0.5 mL cartridge</i>	NEW	2	2	0	<sup>a</sup> Ovaleap
follitropin alfa 300 units (21.84 microgram)/0.5 mL injection, 0.5 mL pen device	6431L	2	2	0	<sup>a</sup> Gonal-f Pen
follitropin alfa 300 units (22 microgram)/0.5 mL injection, 5 x 0.5 mL pen devices	10866X	3	15	0	Bemfola
<b>FOLLITROPIN ALFA 450 UNITS</b>					
<i>follitropin alfa 450 units (33 microgram)/0.75 mL injection, 0.75 mL cartridge</i>	NEW	2	2	0	<sup>a</sup> Ovaleap
follitropin alfa 450 units (32.76 microgram)/0.75 mL injection, 0.75 mL pen device	6432M	2	2	0	<sup>a</sup> Gonal-f Pen
follitropin alfa 450 units (33 microgram)/0.75 mL injection, 5 x 0.75 mL pen devices	10867Y	3	15	0	Bemfola
<b>FOLLITROPIN ALFA 900 UNITS</b>					
<i>follitropin alfa 900 units (66 microgram)/1.5 mL injection, 1.5 mL cartridge</i>	NEW	5	5	0	<sup>a</sup> Ovaleap
follitropin alfa 900 units (65.52 microgram)/1.5 mL injection, 1.5 mL pen device	6433N	5	5	0	<sup>a</sup> Gonal-f Pen
<b>Category / Program:</b> Section 100 – IVF Program					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED) 5027					
<b>Administrative Advice:</b> <b>Biosimilar prescribing policy</b> <i>Prescribing of a biosimilar brand, Bemfola or Ovaleap, is encouraged for treatment naive patients. Encouraging biosimilar prescribing for treatment naive patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (<a href="http://www.health.gov.au/biosimilars">www.health.gov.au/biosimilars</a>).</i>					
<b>Administrative Advice:</b> <i>Pharmaceutical benefits that have the form follitropin alfa cartridge (Ovaleap) and pharmaceutical benefits that have the form follitropin alfa single pen device (Gonal-f Pen) are equivalent for the purposes of substitution.</i>  <i>Where the Ovaleap brand is supplied, the separate pen device is to be supplied by the pharmacist where required. The pen device for the Ovaleap brand can be obtained by contacting the pharmaceutical wholesaler, or, the sponsor directly.</i>					
<b>Indication:</b> Assisted Reproductive Technology					
<b>Clinical criteria:</b> Patient must be receiving medical services as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule					

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<b>FOLLITROPIN ALFA</b>					
<i>follitropin alfa 300 units (22 microgram)/0.5 mL injection, 0.5 mL cartridge</i>	NEW	3	3	5	<sup>a</sup> Ovaleap
<i>follitropin alfa 300 units (21.84 microgram)/0.5 mL injection, 0.5 mL pen device</i>	8713N	3	3	5	<sup>a</sup> Gonal-f Pen
<i>follitropin alfa 450 units (33 microgram)/0.75 mL injection, 0.75 mL cartridge</i>	NEW	3	3	5	<sup>a</sup> Ovaleap
<i>follitropin alfa 450 units (32.76 microgram)/0.75 mL injection, 0.75 mL pen device</i>	8714P	3	3	5	<sup>a</sup> Gonal-f Pen
<i>follitropin alfa 900 units (66 microgram)/1.5 mL injection, 1.5 mL cartridge</i>	NEW	2	2	5	<sup>a</sup> Ovaleap
<i>follitropin alfa 900 units (65.52 microgram)/1.5 mL injection, 1.5 mL pen device</i>	8715Q	2	2	5	<sup>a</sup> Gonal-f Pen
<b>Category / Program:</b> General Schedule					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Restricted benefit					
<b>Administrative Advice:</b> <b>Biosimilar prescribing policy</b> <i>Prescribing of the biosimilar brand, Ovaleap, is encouraged for treatment naive patients. Encouraging biosimilar prescribing for treatment naive patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (<a href="http://www.health.gov.au/biosimilars">www.health.gov.au/biosimilars</a>).</i>					
<b>Administrative Advice:</b> <i>Pharmaceutical benefits that have the form follitropin alfa cartridge (Ovaleap) and pharmaceutical benefits that have the form follitropin alfa single pen device (Gonal-f Pen) are equivalent for the purposes of substitution.</i>  <i>Where the Ovaleap brand is supplied, the separate pen device is to be supplied by the pharmacist where required. The pen device for the Ovaleap brand can be obtained by contacting the pharmaceutical wholesaler, or, the sponsor directly.</i>					
<b>Indication:</b> Anovulatory infertility					
<b>Administrative Advice:</b> Except in cases of hypopituitarism or primary amenorrhoea, the patient should have been adequately treated with clomifene citrate and/or gonadorelin and failed to have conceived.					
<b>Administrative Advice:</b> 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.					
<b>Administrative Advice:</b> Oligomenorrhoea should have been present for at least twelve months or amenorrhoea for at least six months prior to treatment.					
<b>Administrative Advice:</b> Patients with hyperprolactinaemia should have had appropriate surgical or medical treatment prior to treatment.					
<b>Category / Program:</b> General Schedule					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Restricted benefit					
<b>Indication:</b> Infertility					
<b>Clinical criteria:</b>					
The condition must be due to hypogonadotrophic hypogonadism					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be following failure of 6 months' treatment with human chorionic gonadotrophin to achieve adequate spermatogenesis					
<b>AND</b>					
<b>Clinical criteria:</b>					

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The treatment must be administered with human chorionic gonadotrophin
<b>Administrative Advice:</b> Except in cases of hypopituitarism or primary amenorrhoea, the patient should have been adequately treated with clomifene citrate and/or gonadorelin and failed to have conceived.
<b>Administrative Advice:</b> Patients with hyperprolactinaemia should have had appropriate surgical or medical treatment prior to treatment.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

### 4 Comparator

- 4.1 The submission nominated the reference brand of follitropin alfa, Gonal-f, as the main comparator. The PBAC considered this was appropriate.
- 4.2 The submission noted that while Bemfola was another PBS-listed follitropin alfa biosimilar, substitution between Bemfola and Gonal-f was not recommended by the PBAC due to differences in the strengths, number of pens per pack and maximum quantities between the brands. Bemfola is available in packs of 1, 5 and 10 pre-filled pens that are single-use only. The PBAC 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.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

### 5 Consideration of the Evidence

#### ***Sponsor hearing***

- 5.1 There was no hearing for this item.

#### ***Consumer comments***

- 5.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The IVF Directors Group of Australia (IVFDGA) and the Australian and New Zealand Society of Reproductive Endocrinology and Infertility (ANZSREI) were supportive of a PBS-listing for Ovaleap and considered that Ovaleap may broaden scope and choice for patients and prescribers in the management of IVF Stimulation Protocols.
- 5.3 The PBAC noted that all the consumer comments did not support 'a'-flagging 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.
- 5.4 The PBAC noted the views of the IVFDGA that:
  - follitropin alfa (Ovaleap) is not bioidentical to follicle-stimulating hormone (FSH) preparations such as Gonal-f or Puregon.
  - brand substitution at the pharmacy was not supported, as it is unsafe where the patient has received no training in use of the pen and noting the dosages

are different from what the patient would have been given on their supplied protocol sheet.

5.5 The PBAC noted the views of the ANZSREI that:

- the Ovaleap device is different from other follitropin alfa preparations and there are more handling errors with Ovaleap than Gonal-f (Longobardi et al., 2019).
- recent evidence from a meta-analysis (Chua et al., 2021) indicates that rates of live birth are lower with biosimilar preparations versus the reference product Gonal-f.

5.6 The PBAC noted the evidence from Chua et al. 2021 has not been evaluated.

### ***Clinical trials***

5.7 The submission was based on an international, multi-centre, Phase III, randomised, assessor-blind, comparator controlled, parallel group efficacy and safety study (XM17-05) of Ovaleap (referred to as XM17 in the study) in comparison to Gonal-f.

5.8 The clinical trials presented in the submission formed part of the TGA submission to register Ovaleap as a biosimilar to Gonal-f. The TGA Delegate Overview noted that the data presented in TGA submission demonstrated that Ovaleap is similar to the Australian reference product, Gonal-f, with comparable pharmacokinetics, efficacy, safety, and immunogenicity.

5.9 As a Category 3 submission, no evaluation of the clinical evidence was undertaken.

### ***Clinical claim***

5.10 The submission claimed that Ovaleap was biosimilar to Gonal-f. The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonably supported by the data.

### ***Economic analysis***

5.11 The submission presented a cost-minimisation analysis of Ovaleap compared with Gonal-f. The equi-effective doses were estimated as 1.0 I.U. follitropin alfa (Ovaleap) and 1.0 I.U. follitropin alfa (Gonal-f), and by extension (as the PBAC recommended 1.0 I.U. Bemfola and 1.0 I.U. Gonal-f to be equi-effective), 1.0 I.U. follitropin alfa (Ovaleap) and 1.0 I.U. follitropin alfa (Bemfola).

5.12 As a Category 3 submission, the economic analysis was not independently evaluated.

5.13 The submission presented the following key assumptions (Table 1) for the cost-minimisation:

**Table 1: Key assumptions and components of the cost-minimisation approach**

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2 of the submission, effectiveness is assumed to be non-inferior to Gonal-f
Therapeutic claim: safety	Based on evidence presented in Section 2 of the submission, safety is assumed to be non-inferior to Gonal-f
Evidence base	One pivotal direct a trial (Study XM17-05)
Equi-effective doses	Ovaleap 300 I.U. = Gonal-f 300 I.U. Ovaleap 450 I.U. = Gonal-f 450 I.U. Ovaleap 900 I.U. = Gonal-f 900 I.U.
Direct medicine costs	Identical on an I.U.-to-I.U. basis.
Other costs or cost offsets	None

Source: Table 3-1 of the submission

**Drug cost/patient/cycle: \$688.90**

5.14 While the average dose of Ovaleap varies significantly for individual patients, using the average dose from the XM17-05 study (1,535.8 I.U.), the cost for a patient undergoing ART per cycle (including wastage) is \$704.40, \$696.64 and \$688.90 with the 300 I.U., 450 I.U. and 900 I.U. cartridge respectively. The submission did not provide any information on the average cost/dose/patient/cycle for anovulatory infertility and hypogonadotropic hypogonadism.

**Estimated PBS utilisation and financial implications**

5.15 The submission used Gonal-f as a price comparator. The proposed price was based on an I.U.-to-I.U. basis at the ex-manufacturer level.

5.16 The submission used a market share approach to estimate the net financial impact. The submission claimed that the listing of Ovaleap is not expected to grow the market. As such, the submission assumed no additional cost to the Medical Benefits Scheme (MBS).

5.17 The submission stated that, in practice, Ovaleap is expected to substitute Gonal-f and Bemfola. The submission stated that the proposed prices and course of treatment with Ovaleap are identical to Gonal-f and that any substitution by Ovaleap will be cost-neutral. On this basis, the rate of substitution of Bemfola with Ovaleap would likely be similar to that for substitution of Bemfola with Gonal-f.

5.18 The submission claimed a saving to the PBS would occur when Ovaleap substitutes Bemfola due to the increased co-payments of Ovaleap exceeding the increased supply chain costs. It is unclear whether the increased co-payments associated with Gonal-f and Ovaleap will affect the substitution of Bemfola. Given that Ovaleap is not expected to grow the market, these cost savings may not be realised.

5.19 The submission did not comment on the impact of different wastage and broken pack fees between Ovaleap, Gonal-f and Bemfola. Given the variability between individual patient’s dosing, it was difficult to determine the impact.

5.20 The submission estimated that 60,000 to < 70,000 Ovaleap scripts would be supplied over the first six years of listing (500 to < 5,000 in Year 1 to 10,000 to < 20,000 in Year

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6). The submission claimed that the cost of Ovaleap to the PBS/RPBS is expected to be \$70 million to < \$80 million over six years (\$0 to < \$10 million in Year 1 to \$20 million to < \$30 million in Year 6) .The submission estimated that the net financial impact to the PBS/RPBS for the listing of Ovaleap is net cost saving over six years (\$0 to < \$10 million in Year 1 to \$0 to < \$10 million in Year 6).

5.21 Table 2 presents the estimated extent of use, cost of Ovaleap to the PBS/RPBS, and the net financial implications to the PBS/RPBS and MBS. The financial impact to Services Australia will be determined by that agency as part of the post PBAC process.

**Table 2: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed <sup>a</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Drug costs</b>						
Cost to PBS (excl. patient co-payments)	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>5</sup>	\$█ <sup>5</sup>	\$█ <sup>5</sup>	\$█ <sup>6</sup>
Cost to RPBS (excl. patient co-payments)	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>
Less patient co-payments	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>
Cost of affected PBS listings (excl. patient co-payments): Gonal-f and Bemfola	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>
Cost of affected RPBS listings (excl. patient co-payments): Gonal-f and Bemfola	\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>
Less patient co-payments	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>
<b>Estimated net financial implications</b>						
Net cost to PBS	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>
Net cost to RPBS	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>
Net cost to PBS/RPBS	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>
Net cost to MBS	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>
<b>Net cost to Government</b>	<b>-\$█<sup>4</sup></b>	<b>-\$█<sup>4</sup></b>	<b>-\$█<sup>4</sup></b>	<b>-\$█<sup>4</sup></b>	<b>-\$█<sup>4</sup></b>	<b>-\$█<sup>4</sup></b>

<sup>a</sup> The number of scripts was estimated by the submission using a market share approach.

Abbreviations: MBS = Medical Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Source: UCM-Release-3-Workbook-v106 – Ovaleap – Infertility and UCM-Release-3-Workbook-v106 – Ovaleap – ART of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> 10,000 to < 20,000

<sup>4</sup> \$0 to < \$10 million

<sup>5</sup> \$10 million to < \$20 million

<sup>6</sup> \$20 million to < \$30 million

### Quality Use of Medicine

5.22 The submission stated that Ovaleap and Gonal-f share the same manner of administration, strengths, number of units per pack and maximum quantities. Gonal-f is available in packs of one cartridge pre-assembled in a pen with 8, 12 or 20 needles (in 300 I.U., 450 I.U. and 900 I.U. respectively). Ovaleap is available in packs containing 1 cartridge and 10 (in 300 I.U. and 450 I.U.) or 20 needles (in 900 I.U.), for use in

conjunction with a pen device that is provided free to patients. The pre-PBAC response stated that the pen devices will be provided to prescribers at clinics. The pre-PBAC response also indicated that the pen devices are intended to be provided at the time of supply of Ovaleap cartridges. The pre-PBAC response stated that the Ovaleap pen devices will include instructions for loading, priming and use and the packaging of the Ovaleap cartridges clearly identifies that it is for use only with the Ovaleap pen device.

- 5.23 Gonal-f and Ovaleap cartridges can be used more than once as they both contain preservatives. Bemfola is available in packs of 1, 5 and 10 pre-filled pens that are preservative-free and single-use only. A preservative-free formulation may be more suitable to patients with allergies to preservatives. The PBAC noted this was a factor in forming its view that Ovaleap would not be considered equivalent to Bemfola for the purposes of substitution.
- 5.24 The pre-PBAC response confirmed that the Ovaleap pen device can be used with more than one cartridge (i.e. once a cartridge is empty, it can be switched with a full one). The pre-PBAC response considered there was low risk of incorrect dosing with Ovaleap as the same quantities of Ovaleap cartridges and Gonal-f pens would be required to make up a prescribed dose, and both Ovaleap and Gonal-f pen devices dial up the dose in 12.5 I.U. increments.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## **6 PBAC Outcome**

- 6.1 The PBAC recommended the listing of follitropin alfa (Ovaleap) in the form of 300 I.U. in 0.5 mL, 450 I.U. in 0.75 mL and 900 I.U. in 1.5 mL multi-dose cartridges as a biosimilar brand of Gonal-f on the:
- General Schedule (Section 85) as Restricted benefits for anovulatory infertility
  - Section 100 (In Vitro Fertilisation (IVF) Program) as Authority Required (STREAMLINED) benefits for Assisted Reproductive Technology.

The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of Ovaleap would be acceptable if it was cost-minimised against Gonal-f.

- 6.2 The PBAC advised that the equi-effective doses are 1.0 I.U. follitropin alfa (Ovaleap) and 1.0 I.U. follitropin alfa (Gonal-f).
- 6.3 The PBAC considered that the claim of biosimilarity for Ovaleap to Gonal-f was adequately supported by the data. The PBAC noted that the TGA delegate considered that the clinical study XM17-05 demonstrated equivalent efficacy for Ovaleap and Gonal-f with respect to the guideline recommended primary endpoint, 'number of oocytes retrieved' and that the safety and tolerability profile of Ovaleap and Gonal-f were similar.

- 6.4 The PBAC advised that, under Section 101(4AACD) of the *National Health Act 1953*, in the Schedule of Pharmaceutical Benefits, Gonal-f and Ovaleap should be treated as equivalent to each other for the purposes of substitution (i.e. ‘a’ flagged in Schedule with a NOTE stating PBS of one form and PBS of another form are equivalent for the purpose of substitution). 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.
- 6.5 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 study (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.
  - The manner of administration, strengths, number of units per pack and maximum quantities are the same between Ovaleap and Gonal-f.
  - Both Ovaleap and Gonal-f are reusable as they both contain preservatives. However, Ovaleap pens can be reused with a new cartridge whereas Gonal-f pens cannot be reused once the cartridge is empty.
  - The evidence (Chua et al., 2021) presented by organisations in support against a-flagging has 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.
- 6.6 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 different devices appropriately. The PBAC advised that the sponsor should work with key bodies such as the IVFDGA and the ANZSREI 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 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.
- 6.7 The PBAC considered that the following administrative note should be included in the Ovaleap listings as follows:

*Where the Ovaleap brand is supplied, the separate pen device is to be supplied to the patient where required as it is not packaged with the cartridges. The pen device for the*

*Ovaleap brand can be obtained by contacting the pharmaceutical wholesaler, or, the sponsor directly.*

- 6.8 The PBAC considered that the biosimilar uptake drivers should be applied to Ovaleap, including the application of the 'Biosimilar prescribing policy' administrative note encouraging the use of biosimilar brands for treatment naïve patients:

*Prescribing of the biosimilar brand, Bemfola or Ovaleap, is encouraged for treatment naïve patients.*

*Encouraging biosimilar prescribing for treatment naïve patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage ([www.health.gov.au/biosimilars](http://www.health.gov.au/biosimilars)).*

- 6.9 The PBAC did not recommend lowering the category of prescribing authority for follitropin alfa under the Section 100 IVF Program from STREAMLINED authority to Restricted benefit. The PBAC noted that listings under Section 100 IVF Program require a STREAMLINED authority and considered that the proposed change to the category was unlikely to influence uptake of Ovaleap.
- 6.10 The PBAC noted that the submission estimated net overall savings to the PBS over the first six years of listing. The PBAC considered that several factors including the increased co-payments associated with Gonal-f and Ovaleap and the presence of preservatives may affect Bemfola substitution. The PBAC considered that Ovaleap would not increase the current market, therefore the projected savings were not likely to be realised.
- 6.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Ovaleap is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over Gonal-f, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 6.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## **7 Recommended listing**

- 7.1 Add new trade product (Ovaleap) as follows:
- 7.2 Add equivalence indicators to the trade products 'Ovaleap' and 'Gonal-f Pen' as follows:

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<b>FOLLITROPIN ALFA</b>					
follitropin alfa 300 units (22 microgram)/0.5 mL injection, 0.5 mL cartridge	NEW	2	2	0	<sup>a</sup> Ovaleap
follitropin alfa 300 units (21.84 microgram)/0.5 mL injection, 0.5 mL pen device	6431L	2	2	0	<sup>a</sup> Gonal-f Pen
follitropin alfa 300 units (22 microgram)/0.5 mL injection, 5 x 0.5 mL pen devices	10866X	3	15	0	Bemfola
<b>FOLLITROPIN ALFA 450 UNITS</b>					
follitropin alfa 450 units (33 microgram)/0.75 mL injection, 0.75 mL cartridge	NEW	2	2	0	<sup>a</sup> Ovaleap
follitropin alfa 450 units (32.76 microgram)/0.75 mL injection, 0.75 mL pen device	6432M	2	2	0	<sup>a</sup> Gonal-f Pen
follitropin alfa 450 units (33 microgram)/0.75 mL injection, 5 x 0.75 mL pen devices	10867Y	3	15	0	Bemfola
<b>FOLLITROPIN ALFA 900 UNITS</b>					
follitropin alfa 900 units (66 microgram)/1.5 mL injection, 1.5 mL cartridge	NEW	5	5	0	<sup>a</sup> Ovaleap
follitropin alfa 900 units (65.52 microgram)/1.5 mL injection, 1.5 mL pen device	6433N	5	5	0	<sup>a</sup> Gonal-f Pen
<b>Restriction Summary / Treatment of Concept: 5027 (as per Gonal-F brand as at 1 July 2021)</b>					
	<b>Category / Program:</b> Section 100 – IVF Program				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED) 5027				
	<p><b>Administrative Advice:</b>  <b>Biosimilar prescribing policy</b>                      Prescribing of a biosimilar brand, Bemfola or Ovaleap, is encouraged for treatment naive patients. Encouraging biosimilar prescribing for treatment naive patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (<a href="http://www.health.gov.au/biosimilars">www.health.gov.au/biosimilars</a>).</p>				
	<p><b>Administrative Advice:</b>                      Pharmaceutical benefits that have the form follitropin alfa cartridge (Ovaleap) and pharmaceutical benefits that have the form follitropin alfa single pen device (Gonal-f Pen), in the same corresponding strength, are equivalent for the purposes of substitution.</p> <p>Where the Ovaleap brand is supplied, the separate pen device is to be supplied to the patient where required as it is not packaged with the cartridges. The pen device for the Ovaleap brand can be obtained by contacting the pharmaceutical wholesaler, or, the sponsor directly.</p>				
	<b>Indication:</b> Assisted Reproductive Technology				
	<b>Clinical criteria:</b>				
	Patient must be receiving medical services as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule				

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<b>FOLLITROPIN ALFA</b>					
follitropin alfa 300 units (22 microgram)/0.5 mL injection, 0.5 mL cartridge	NEW	3	3	5	<sup>a</sup> Ovaleap
follitropin alfa 300 units (21.84 microgram)/0.5 mL injection, 0.5 mL pen device	8713N	3	3	5	<sup>a</sup> Gonal-f Pen
<b>follitropin alfa 450 units (33 microgram)/0.75 mL injection, 0.75 mL cartridge</b>					
follitropin alfa 450 units (33 microgram)/0.75 mL injection, 0.75 mL cartridge	NEW	3	3	5	<sup>a</sup> Ovaleap
follitropin alfa 450 units (32.76 microgram)/0.75 mL injection, 0.75 mL pen device	8714P	3	3	5	<sup>a</sup> Gonal-f Pen
<b>follitropin alfa 900 units (66 microgram)/1.5 mL injection, 1.5 mL cartridge</b>					
follitropin alfa 900 units (66 microgram)/1.5 mL injection, 1.5 mL cartridge	NEW	2	2	5	<sup>a</sup> Ovaleap
follitropin alfa 900 units (65.52 microgram)/1.5 mL injection, 1.5 mL pen device	8715Q	2	2	5	<sup>a</sup> Gonal-f Pen
<b>Restriction Summary / Treatment of Concept: 6257 (as per Gonal-F brand as at 1 July 2021)</b>					
<b>Category / Program:</b> General Schedule					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Restricted benefit					
<b>Administrative Advice:</b> <b>Biosimilar prescribing policy</b> Prescribing of the biosimilar brand, Bemfola or Ovaleap, is encouraged for treatment naive patients. Encouraging biosimilar prescribing for treatment naive patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage ( <a href="http://www.health.gov.au/biosimilars">www.health.gov.au/biosimilars</a> ).					
<b>Administrative Advice:</b> Pharmaceutical benefits that have the form follitropin alfa cartridge (Ovaleap) and pharmaceutical benefits that have the form follitropin alfa single pen device (Gonal-f Pen), in the same corresponding strength, are equivalent for the purposes of substitution.  Where the Ovaleap brand is supplied, the separate pen device is to be supplied to the patient where required as it is not packaged with the cartridges. The pen device for the Ovaleap brand can be obtained by contacting the pharmaceutical wholesaler, or, the sponsor directly.					
<b>Indication:</b> Anovulatory infertility					
<b>Administrative Advice:</b> Except in cases of hypopituitarism or primary amenorrhoea, the patient should have been adequately treated with clomifene citrate and/or gonadorelin and failed to have conceived.					
<b>Administrative Advice:</b> 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.					
<b>Administrative Advice:</b> Oligomenorrhoea should have been present for at least twelve months or amenorrhoea for at least six months prior to treatment.					
<b>Administrative Advice:</b> Patients with hyperprolactinaemia should have had appropriate surgical or medical treatment prior to treatment.					
<b>Restriction Summary / Treatment of Concept: 6321 Restricted benefit (as per Gonal-F brand as at 1 July 2021)</b>					
<b>Category / Program:</b> General Schedule					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Restricted benefit					
<b>Indication:</b> Infertility					
<b>Clinical criteria:</b>					

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	The condition must be due to hypogonadotropic hypogonadism
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be following failure of 6 months' treatment with human chorionic gonadotrophin to achieve adequate spermatogenesis
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be administered with human chorionic gonadotrophin
	<b>Administrative Advice:</b> Except in cases of hypopituitarism or primary amenorrhoea, the patient should have been adequately treated with clomifene citrate and/or gonadorelin and failed to have conceived.
	<b>Administrative Advice:</b> Patients with hyperprolactinaemia should have had appropriate surgical or medical treatment prior to treatment.

7.3 Flow-on changes to Gonal-f and Bemfola to reflect the presence of a second biosimilar brand , are summarised as follows:

<b>Restriction Summary / Treatment of Concept: 5027 Authority Required (Streamlined) (current as at 1 July 2021)</b>	
	<b>Category / Program:</b> Section 100 (IVF Treatment)
	<b>MEDICINAL PRODUCT:</b> FOLLITROPIN ALFA
	<b>medicinal product pack (Trade product):</b>
	<b>PBS item code</b>
	follitropin alfa 300 units (21.84 microgram)/0.5 mL injection, 0.5 mL pen device (Gonal F 300) 6431L
	follitropin alfa 450 units (32.76 microgram)/0.75 mL injection, 0.75 mL pen device (Gonal F 450) 6432M
	follitropin alfa 900 units (65.52 microgram)/1.5 mL injection, 1.5 mL pen device (Gonal F 900) 6433N
	follitropin alfa 75 units (5.5 microgram)/0.125 mL injection, 5 x 0.125 mL pen devices (Bemfola 75) 10861P
	follitropin alfa 150 units (11 microgram)/0.25 mL injection, 5 x 0.25 mL pen devices (Bemfola 150) 10873G
	follitropin alfa 225 units (16.5 microgram)/0.375 mL injection, 5 x 0.375 mL pen devices (Bemfola 225) 10872F
	follitropin alfa 300 units (22 microgram)/0.5 mL injection, 5 x 0.5 mL pen devices (Bemfola 300) 10866X
	follitropin alfa 450 units (33 microgram)/0.75 mL injection, 5 x 0.75 mL pen devices (Bemfola 450) 10867Y
	<b>Indication:</b> Assisted Reproductive Technology
	<b>Administrative Advice:</b> <b>Biosimilar prescribing policy</b> <del>Prescribing of the biosimilar brand, Bemfola, is encouraged for treatment naive patients.</del> <del>Encouraging biosimilar prescribing for treatment naive patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (www.health.gov.au/biosimilars).</del>
	<b>Administrative Advice:</b> <b>Biosimilar prescribing policy</b> <i>Prescribing of a biosimilar brand, Bemfola or Ovaleap, is encouraged for treatment naive patients.</i> <i>Encouraging biosimilar prescribing for treatment naive patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (www.health.gov.au/biosimilars).</i>
	<b>Administrative Advice:</b> <i>Pharmaceutical benefits that have the form follitropin alfa cartridge (Ovaleap) and pharmaceutical benefits that have the form follitropin alfa single pen device (Gonal-f Pen), in the same corresponding strength, are equivalent for the purposes of substitution.</i>

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Where the Ovaleap brand is supplied, the separate pen device is to be supplied to the patient where required as it is not packaged with the cartridges. The pen device for the Ovaleap brand can be obtained by contacting the pharmaceutical wholesaler, or, the sponsor directly.
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<b>Restriction Summary / Treatment of Concept: 6257</b> (current as at 1 July 2021)	<b>Indication 14538:</b> Anovulatory infertility
<b>Restriction Summary / Treatment of Concept: 6321</b> (current as at 1 July 2021)	<b>Indication 14563:</b> Infertility
<b>Category / Program:</b> General Schedule	
<b>MEDICINAL PRODUCT:</b> FOLLITROPIN ALFA	
<b>medicinal product pack (Trade product):</b>	<b>PBS item code</b>
follitropin alfa 300 units (21.84 microgram)/0.5 mL injection, 0.5 mL pen device (Gonal F 300)	8713N
follitropin alfa 450 units (32.76 microgram)/0.75 mL injection, 0.75 mL pen device (Gonal F 450)	8714P
follitropin alfa 900 units (65.52 microgram)/1.5 mL injection, 1.5 mL pen device (Gonal F 900)	8715Q
follitropin alfa 75 units (5.5 microgram)/0.125 mL injection, 5 x 0.125 mL pen devices (Bemfola 75)	10865W
follitropin alfa 150 units (11 microgram)/0.25 mL injection, 5 x 0.25 mL pen devices (Bemfola 150)	10877L
follitropin alfa 225 units (16.5 microgram)/0.375 mL injection, 5 x 0.375 mL pen devices (Bemfola 225)	10876K
<i>Note that Bemfola 300 and Bemfola 450 are not currently PBS listed for these 2 PBS indications.</i>	
<b>Administrative Advice:</b> <b>Biosimilar prescribing policy</b> <i>Prescribing of the biosimilar brand, Bemfola, is encouraged for treatment naive patients. Encouraging biosimilar prescribing for treatment naive patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (<a href="http://www.health.gov.au/biosimilars">www.health.gov.au/biosimilars</a>).</i>	
<b>Administrative Advice:</b> <b>Biosimilar prescribing policy</b> <i>Prescribing of a biosimilar brand, Bemfola or Ovaleap, is encouraged for treatment naive patients. Encouraging biosimilar prescribing for treatment naive patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (<a href="http://www.health.gov.au/biosimilars">www.health.gov.au/biosimilars</a>).</i>	
<b>Administrative Advice:</b> <i>Pharmaceutical benefits that have the form follitropin alfa cartridge (Ovaleap) and pharmaceutical benefits that have the form follitropin alfa single pen device (Gonal-f Pen), in the same corresponding strength, are equivalent for the purposes of substitution.  Where the Ovaleap brand is supplied, the separate pen device is to be supplied to the patient where required as it is not packaged with the cartridges. The pen device for the Ovaleap brand can be obtained by contacting the pharmaceutical wholesaler, or, the sponsor directly.</i>	

***These restrictions may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **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.