

**5.12 TRIPTORELIN
100 microgram in 1 mL (as acetate), pre-filled syringe,
Decapeptyl®, Ferring Pharmaceuticals Pty Ltd.**

1 Purpose of Application

1.1 The submission requested a Section 100 (IVF Program) listing for triptorelin acetate for down-regulation and prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) as part of an Assisted Reproductive Technology (ART) treatment program.

2 Requested listing

2.1 The requested listing is shown in the following table.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
TRIPTORELIN ACETATE 100 micrograms/1mL injection, 28 x 1 1mL pre-filled syringes		0	\$ [REDACTED]	Decapeptyl	Ferring

Category / Program	Section 100 – IVF
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Assisted Reproductive Technology
Treatment phase:	-
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be for prevention of premature luteinisation and ovulation, AND Patient must be undergoing controlled ovarian stimulation, AND Patient must be receiving medical services as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule.

2.2 The basis for listing is cost-minimisation against nafarelin.

3 Background

- 3.1 Triptorelin acetate was TGA registered on 26 February 2015 for down-regulation and prevention of premature LH surges in women undergoing COH as part of an ART treatment program. Triptorelin acetate was registered on the basis of Phase II clinical data.
- 3.2 Triptorelin acetate has not been considered by the PBAC previously.
- 3.3 Three gonadotropin-releasing hormone (GnRH) analogues are listed on the Section 100 IVF program, nafarelin, ganirelix and cetrorelix. Ganirelix was recommended for listing at the same price as nafarelin for the treatment of endometriosis. For ART, nafarelin and cetrorelix were recommended for listing on a cost-minimisation basis compared with ganirelix.

4 Clinical place for the proposed therapy

- 4.1 GnRH analogues are used in women undergoing ART to prevent the surge in natural LH and hence to prevent premature ovulation and allow oocyte collection. Nafarelin is a GnRH agonist and is generally used in a long down-regulation protocol with treatment started in the mid-luteal phase (day 21-23 of the previous menstrual cycle). Ganirelix and cetrorelix are GnRH antagonists used in a short-down-regulation protocol with treatment started in the follicular phase (day 5-6 of the cycle).
- 4.2 Triptorelin acetate is proposed as an alternative GnRH agonist.

5 Comparator

- 5.1 The submission nominated nafarelin as the main comparator. Ganirelix was nominated as a secondary clinical comparator because (i) nafarelin was recommended for listing on a cost-minimisation basis versus ganirelix and (ii) ganirelix is the most commonly used GnRH analogue in Australia.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on an indirect comparison of triptorelin acetate and nafarelin using ganirelix as the common reference. As part of the indirect comparison, a head-to-head comparison of triptorelin acetate and ganirelix was also presented.

6.4 Details of the trials presented in the submission are provided in the table.

Table 1: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Triptorelin acetate vs ganirelix		
EMEOSG 2001	European and Middle East Orgalutran Study Group. Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation.	Human Reproduction. 2001; 16(4): 644-651
Nafarelin vs ganirelix		
Rombauts 2006	Rombauts, L., D. Healy, R. J. Norman, A. Speirs, B. Watkins, J. Yovich, R. Norman, M. Bowman, G. Driscoll, S. Lindenberg, Z. Kilani, P. O. Dale, B. J. Oddens, H. G. van Hooren and B. M. J. L. Mannaert. A comparative randomised trial to assess the impact of oral contraceptive pre-treatment on follicular growth and hormone profiles in GnRH antagonist-treated patients.	Human Reproduction. 2006; 21(1): 95-103

Source: Table B-4 p25 of the submission.

6.5 The key features of the randomised trials are summarised in the table below.

Table 2: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Triptorelin acetate vs ganirelix					
EMEOSG 2001	337	R, OL, ≥12-16 weeks after embryo transfer	Low	Females of infertile couples undergoing IVF treatment	No. of oocytes retrieved, No. of good quality embryos (Grade I and II), Ongoing pregnancy.
Nafarelin vs ganirelix					
Rombauts 2006	222	R, OL, ≥12-16 weeks after embryo transfer	Low	Females of infertile couples undergoing IVF treatment	No. of oocytes retrieved, No. of good quality embryos (Grade I and II), Ongoing pregnancy.

Source: compiled during the evaluation
Abbreviations: OL=open label; R=randomised

6.6 There were a number of potential exchangeability issues due to differences across the trials with respect to patient demographics, duration and cause of infertility and concomitant use of rFSH. In the ganirelix arms, the number of oocytes and good quality embryos per attempt were lower in EMEOSG 2001 compared with Rombauts 2006 however, the ongoing pregnancy rate was higher in EMEOSG 2001 compared with Rombauts 2006.

6.7 The ESC noted that the data presented was limited, which made comparisons difficult, particularly when assessing harms. The PSCR (p.1) acknowledged that there were differences in the recruited trial populations between the studies, but contends that the submitted indirect comparison remains the best approach possible.

Comparative effectiveness

- 6.8 A summary of the comparative effectiveness for triptorelin acetate versus nafarelin is presented in Table 3.
- 6.9 The mean difference in the number of oocytes per attempt for triptorelin acetate minus nafarelin was 0.3 (95% CI: -2.28, 2.88). Based on a non-inferiority margin of 3, the submission claimed that triptorelin acetate is non-inferior to nafarelin.
- 6.10 The difference in the proportion of patients with an ongoing pregnancy with triptorelin acetate compared with nafarelin was not statically significant. The mean difference for triptorelin acetate minus nafarelin was 0.03% (95% CI: -15.4% to 15.4%). The lower confidence interval exceeds the 10% non-inferiority margin previously accepted by the PBAC. The Pre-Sub-Committee Response (PSCR) (p.2) stated this is not surprising in the indirect comparison given that the Rombauts 2006 study was not powered for the outcome of ongoing pregnancy, and that it should be noted that triptorelin met the 10% non-inferiority margin for the difference in ongoing pregnancy rate when directly compared with ganirelix.
- 6.11 The mean adjusted difference in the proportion of patients with an ongoing pregnancy for triptorelin acetate minus ganirelix was 2.5% (95% CI -8.0%, 13.0%). The lower 95% confidence limit is within the 10% non-inferiority margin previously accepted by the PBAC.
- 6.12 The ESC noted that the most clinically and patient relevant outcome is live birth rate, however it is not often reported. The ESC considered that while oocytes recovered is relevant, ongoing pregnancy rate is a more relevant outcome.

Table 3: Summary of comparative benefits for triptorelin acetate and nafarelin/ganirelix

Benefits								
Continuous Outcome I: No. of oocytes recovered per attempt [indirect comparison]								
Trial	Active treatment group (triptorelin acetate/nafarelin)			Common arm comparator (ganirelix)			Indirect comparison: Mean difference* Triptorelin acetate vs nafarelin (95% CI)	
	n	Mean number	SD	n	Mean number	SD		
EMEOSG 2001	111	9.6	6.8	226	7.9	5.1	(RD) 0.3 (-2.28, 2.88)	
Rombauts 2006	111	12.9	8.7	110	11.5	7.6		
Continuous Outcome I: No. of good quality (grade I and II) embryos per attempt [indirect comparison]								
EMEOSG 2001	111	2.9	NR	226	2.7	NR	(RD) -0.4 (-1.73, 0.93)	
Rombauts 2006	111	5.7	4.3	110	5.0	4.5		
Dichotomous Outcome I: Ongoing pregnancy rate per attempt [indirect comparison]								
	Triptorelin acetate	Ganirelix	Nafarelin	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					Triptorelin acetate	Ganirelix	Nafarelin	
EMEOSG 2001	37/109	70/226	-	1.10 (0.79, 1.52)	33.9	31.0	-	2.5% (-8.0%, 13.0%)
Rombauts 2006	-	23/110	26/109	1.14 (0.70, 1.87)	-	20.9	23.9	2.9% (-8.1%, 14.0%)
Indirect comparison: EMEOSG 2001 vs Rombauts 2006				0.96 (0.53, 1.72)	-			0.03% (-15.4%, 15.4%)

Source: submission Table B-27 p73, p73, Table B-29 p75; values in italics calculated during the evaluation

Abbreviations: OHSS = ovarian hyperstimulation syndrome; RR = risk difference; RR = risk ratio; SD = standard deviation.

* Event rate is based on one cycle of IVF treatment.

Comparative harms

- 6.13 The submission did not present a comparison of safety outcomes for triptorelin acetate versus nafarelin.
- 6.14 The incidence of AEs in the ganirelix treatment group in Rombauts 2006 was higher than in the ganirelix group in EMEOSG 2001 (44.0% vs 22.6%). This impacts the indirect comparison; however the increase in AEs with nafarelin versus ganirelix was numerically larger than the increase with triptorelin versus ganirelix.
- 6.15 The incidence of SAEs and OHSS events was relatively low and the individual trials were not powered to detect differences. In EMEOSG 2001, none of the SAEs were reported to be related to treatment and all patients recovered from the event. In Rombauts 2006, four of the SAEs were considered to be related to treatment (one ovarian cyst and one case of OHSS in the OC+ganirelix group; one case of OHSS in nafarelin group and one ectopic pregnancy in the ganirelix group). In EMEOSG 2001 there was one (0.9%) OHSS event in the triptorelin acetate group compared with four (1.8%) in the ganirelix group. In Rombauts 2006 there were six (5.4%) OHSS events in the nafarelin group compared with two (1.8%) in the ganirelix group.
- 6.16 The ESC noted the difficulty in comparing safety outcomes for triptorelin and nafarelin through the common comparator, as ganirelix is used in short stimulation cycles, and triptorelin and nafarelin are used in long stimulation cycles and have

different rates of serious adverse effects, including ovarian hyperstimulation syndrome.

Table 4: Summary of comparative harms for triptorelin acetate and nafarelin/ganirelix

Harms						
	Triptorelin acetate/nafarelin	Ganirelix	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Triptorelin acetate/nafarelin	Ganirelix	
Adverse events						
EMEOSG 2001	30/111	51/226	<i>1.20</i> <i>(0.81, 1.77)</i>	27.0	22.6	<i>4.5%</i> <i>(-5.4%, 14.4%)</i>
Rombauts 2006	75/111	48/109	<i>1.53</i> <i>(1.20, 1.97)</i>	67.6	44.0	<i>23.5%</i> <i>(10.8%, 36.3%)</i>
Serious adverse events						
EMEOSG 2001	<i>3/111</i>	<i>7/226</i>	<i>0.87</i> <i>(0.23, 3.31)</i>	2.7	3.1	<i>-0.4%</i> <i>(-4.2%, 3.4%)</i>
Rombauts 2006	4/111	3/109	<i>1.31</i> <i>(0.30, 5.71)</i>	3.6	2.8	<i>0.9%</i> <i>(-3.8%, 5.5%)</i>
Ovarian hyperstimulation (OHSS) events						
EMEOSG 2001	1/111	4/226	<i>0.51</i> <i>(0.06, 4.50)</i>	0.9	1.8	<i>0.9%</i> <i>(-3.3%, 1.6%)</i>
Rombauts 2006	6/111	2/111	<i>3.00</i> <i>(0.62, 14.54)</i>	5.4	1.8	<i>3.6%</i> <i>(-1.3%, 8.5%)</i>

Source: submission Table B-27 p73, p73, Table B-29 p75; values in italics calculated during the evaluation

Abbreviations: OHSS = ovarian hyperstimulation syndrome; RR = risk difference; RR = risk ratio; SD = standard deviation.

* Event rate is based on one cycle of IVF treatment.

Clinical claim

- 6.17 The submission described triptorelin as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over the primary comparator, nafarelin.
- 6.18 The ESC agreed that the claim may be reasonable for the number of oocytes retrieved but not for the more clinically relevant outcome of ongoing pregnancies. Data are not available for the number of live births.
- 6.19 Based on the safety comparison undertaken during the evaluation, the safety of triptorelin acetate and nafarelin appears similar, however, this is based on an indirect comparison and the trials were not powered for safety outcomes. The ESC considered that it was likely that triptorelin and nafarelin had similar rates of serious adverse events and ovarian hyperstimulation events, noting however that data to make a comparison was limited.
- 6.20 The submission described triptorelin as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over the clinical comparator, ganirelix. The claim for efficacy is adequately supported. The safety of triptorelin acetate and ganirelix appears similar; however, the trial was not powered for safety outcomes.
- 6.21 The PBAC considered that the claim of non-inferior effectiveness may be reasonable.
- 6.22 The PBAC considered that the claim of non-inferior safety may be reasonable, noting that there was limited data on which to base a comparison.

Economic analysis

- 6.23 The equi-effective doses are estimated as triptorelin acetate 100 microgram daily and nafarelin 800 microgram daily over an ART treatment cycle. The equi-effective doses are based on the fixed doses used in the trials presented. These doses are the same as recommended in the Product Information documents.
- 6.24 The submission assumed the duration of treatment with triptorelin acetate is the same as with nafarelin. This appears reasonable based on the trial data (median of 26 days with triptorelin acetate and mean of 27 days with nafarelin) however; limited data were available to enable a robust comparison of the treatment durations.
- 6.25 The submission assumed there were no material changes in the patterns of other therapies. rFSH is used concomitantly with triptorelin acetate and nafarelin. The initial dose of rFSH differed across the trials (EMESOG 2001, 150 IU; Rombauts 2006, 200 IU). After 5-6 days the rFSH dose was individualised depending on the ovarian response (follicular growth) as assessed by ultrasound. The large difference across the trials in the total rFSH doses in the ganirelix arms (EMEOSG 2001: 1350 IU; Rombauts 2006: 1966 IU) prevented a meaningful comparison of the concomitant rFSH dose used with triptorelin acetate versus nafarelin.
- 6.26 The requested price for 28 x 100 microgram syringes of triptorelin acetate (AEMP \$212.00) is the same as for 2 x 60 x 200 microgram actuations of nafarelin.

6.27 The duration of treatment with triptorelin acetate and nafarelin is variable depending on response. The proposed maximum quantity for triptorelin acetate provides 28 days of treatment. The maximum quantity for nafarelin provides 30 days of treatment. A proportion of patients treated with triptorelin acetate or nafarelin are likely to require a second prescription. The cost of treatment with triptorelin acetate and nafarelin for different treatment durations is presented in Table 5. The cost of triptorelin acetate per cycle is higher than the cost of nafarelin for patients treated for 29 or 30 days, and for patients treated for 31-45 days if only 1 pack of nafarelin is prescribed. The calculations assume broken packs are not dispensed to the patient.

Table 5: Comparator pricing and cost per cycle for different treatment durations

	Maximum quantity	Supply	AEMP	\$AEMP/cycle ^a			
				≤ 28 days	29 – 30 days	31-45 days	
						Min disp. ^b	Max disp. ^b
Nafarelin 200 mcg, 60 actuations	2	30 days	\$212.00	1 script [2 packs] \$212	1 script [2 packs] \$212	2 scripts [3 packs] \$318	2 scripts [4 packs] \$414
Triptorelin 100 mcg, 28 syringes	1	28 days	\$212.00	1 script [1 packs] \$212	2 scripts [2 packs] \$414	2 scripts [2 packs] \$414	2 scripts [2 packs] \$414

Source: Table E-1 p87 and Table E-2 p 87 of the submission. Text in *italics* was compiled during the evaluation

Abbreviations: AEMP = approved ex-manufacturer price.

^a A cycle is based on duration of treatment.

^b The ranges presented are based on the minimum and maximum number units dispensed to patients. The calculations assume packs are not broken.

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

6.28 For patients requiring ≤28 days of treatment, the dispensed cost of triptorelin acetate is \$ [REDACTED] per patient per ART cycle. For patients requiring ≤30 days of treatment, the dispensed cost of nafarelin is \$ [REDACTED] per patient per ART cycle.

Estimated PBS usage & financial implications

6.29 This submission was not considered by DUSC. A summary of the estimated use and financial implications for listing triptorelin acetate on the PBS is presented in Table 6.

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
GnRH agonist scripts	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Triptorelin acetate market share	9%	27%	45%	45%	45%
Triptorelin acetate scripts	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to PBS/RPBS					
Triptorelin acetate	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Nafarelin	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost	\$0	\$0	\$0	\$0	\$0

Source: Table E-4 p88, Table E-5 p89, Table E-6 p89, Table E-11 p91 of the submission.

6.30 The submission assumed that one script of triptorelin acetate 100 microgram x 28 will replace one script of nafarelin 200 microgram x 60 sprays x 2. Patients requiring 29 or 30 days of treatment would require a second script of triptorelin acetate but not nafarelin. In addition, for patients requiring 31-45 days of treatment, one pack of

nafarelin could be prescribed (as opposed to the maximum quantity of two spray bottles) which would be half the cost of a pack of triptorelin acetate. It is unknown how many patients would require a second script of triptorelin acetate or nafarelin. Assuming 10% of patients require 29-30 days of treatment and 10% 31-45 days of treatment, the additional PBS cost would be of approximately less than \$10 million in year 5.

- 6.31 The ESC considered there was wastage was a risk, with a reasonable number of patients requiring between 29 and 41 days of treatment and potential difficulties with the dispensing of broken packs in a community pharmacy setting.

Quality Use of Medicines

- 6.32 The submission stated activities are in place to support quality use of medicines.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of triptorelin (as acetate) for assisted reproductive technology (ART) under Section 100 (IVF Program) on a cost-minimisation basis with nafarelin, where the equi-effective doses are triptorelin 100 micrograms (as acetate) daily and nafarelin 800 micrograms (base) daily over an ART treatment cycle.
- 7.2 The PBAC considered that the submission's nominated main comparator, nafarelin, was appropriate.
- 7.3 The PBAC considered that there were a number of potential exchangeability issues with the indirect comparison of triptorelin (EMEOSG 2001) and nafarelin (Rombauts 2006), using ganirelix as the common reference, including the patient demographics, duration and cause of infertility, and the concomitant use of rFSH. The PBAC noted that the patient relevant outcome of live births was not reported in the studies. The PBAC noted that for the primary outcome of number of oocytes retrieved, triptorelin fell within the non-inferiority margin of 3 in the indirect comparison with nafarelin. For the outcome of ongoing pregnancy, the PBAC noted that the lower confidence interval exceeds the 10% non-inferiority margin previously accepted by the PBAC, however considered that the Rombauts 2006 trial was not powered for the outcome of ongoing pregnancies. The PBAC further noted that in the EMEOSG 2001 trial of a direct comparison of triptorelin and ganirelix, triptorelin fell within the 10% non-inferiority margin for the outcome of ongoing pregnancies. The PBAC recalled that nafarelin and cetrorelix were recommended for ART on a cost-minimisation basis compared with ganirelix.
- 7.4 The PBAC considered that it was likely that triptorelin and nafarelin had similar rates of serious adverse events and ovarian hyperstimulation events, noting however that data to make a comparison was limited.
- 7.5 The PBAC considered that the data presented in the submission suggested that triptorelin is very likely to be non-inferior in terms of comparative effectiveness and safety compared to nafarelin.

- 7.6 The PBAC considered that wastage is a potential issue for the 28 syringe pack, and expressed a preference for the sponsor's proposal to list the smaller pack size of 7 with a maximum quantity of four packs.
- 7.7 The PBAC noted that the listing of triptorelin would be cost-neutral to the PBS as it would substitute for nafarelin.
- 7.8 The PBAC recommended that triptorelin should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.9 The PBAC advised that triptorelin is not suitable for prescribing by nurse practitioners.
- 7.10 The PBAC recommended that the Early Supply Rule should not apply.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
TRIPTORELIN ACETATE 100 micrograms/1mL injection, 7 x 1mL pre-filled syringes	4	0	Decapeptyl	Ferring

Category / Program	Section 100 – IVF
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Assisted Reproductive Technology
Treatment phase:	-
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

Clinical criteria:	The treatment must be for prevention of premature luteinisation and ovulation, AND Patient must be undergoing controlled ovarian stimulation, AND Patient must be receiving medical services as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule.
--------------------	--

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Ferring welcomes the PBAC decision to recommend listing of DECAPEPTYL for use in ART under Section 100 (IVF Program).