PUBLIC SUMMARY DOCUMENT

Product: PROGESTERONE, pessary, 100 mg, Endometrin®
Sponsor: Ferring Pharmaceuticals Pty Ltd
Date of PBAC Consideration: March 2014

1. Purpose of Application

The major submission requested listing of a new item under the Section 100, IVF/GIFT Program for luteal phase support in patients meeting certain criteria as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.

2. Background

This product had not previously been considered by the PBAC.

3. Registration Status

Endometrin was TGA registered on 19 September 2012 for luteal support as part of an Assisted Reproductive Technology (ART) treatment programme for infertile women.

4. Listing Requested and PBAC's View

Section 100 (IVF/GIFT treatment)

Criteria for availability
For luteal phase support in patients who are receiving medical treatment as described in items 13200 or 13201 of the Medicare Benefits Schedule. The luteal phase is defined as the time span from embryo transfer until implantation confirmed by positive β-hCG measurement.

Note
Supply of these items is through an accredited IVF/GIFT clinic.

Listing was requested on a cost-minimisation basis with the nominated comparators, progesterone gel (Crinone®) and the Oripro® brand of progesterone pessaries.

The PBAC noted that the requested listing was consistent with the nominated comparators.

5. Clinical Place for the Proposed Therapy

Progesterone is a steroid secreted by the ovary, placenta, and adrenal gland. In the presence of adequate oestrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.

Endometrin was proposed to offer an alternative treatment option for patients currently receiving vaginal progesterone for luteal phase support in ART.

The clinical management algorithm for the intended use of Endometrin and for current practice concurs with the Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines. The clinical management algorithm also coincides with the management algorithm of the main comparators.

6. Comparator

The submission nominated progesterone gel 8% (Crinone) and progesterone pessaries 100 mg and 200 mg (Oripro) as the main comparators.

The PBAC agreed that these were the appropriate comparators.

7. Clinical Trials

The submission was based on one head-to-head randomised trial (Trial 2004-02) comparing Endometrin pessaries 100 mg (twice a day), to Endometrin pessaries 100 mg three times a day to 90 mg progesterone gel once daily. Publication details are presented in the table below. No trials were identified that compared Endometrin with Oripro pessaries and no trials were excluded by the submission.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
2004-02 Study Doody, K et al	2004-02 Endometrin for luteal phase support in a randomized, controlled, open-label, prospective in-vitro fertilization trial using a combination of Menopur and Bravelle for controlled ovarian hyperstimulation	July 2006 Fertility and Sterility 2009; Vol 91, Issue 4.

The PBAC noted that in the clinical trial 2004-02, Endometrin pessaries and progesterone gel were used for a 10-week period, continuing on after the luteal support phase. The submission proposed the use of Endometrin in the luteal phase only, which is approximately 2 weeks. This proposal is consistent with the restrictions of the comparators.

8. Results of Trials

Ongoing pregnancy was measured in the trial as the primary outcome. Live birth rates and biochemical pregnancy rates were measured in the trial as secondary outcomes.

The results from the trial are shown in the tables below.

Results of the primary outcome, ongoing pregnancy in Trial 2004-02

	Endometrin 100 mg bid	Endometrin 100 mg tid	Progesterone gel qd
ITT Population	**(N=404)**	**(N=404)**	**(N=403)**
Pregnancy Rate	156 (39%)	171 (42%)	170 (42%)
95% CI	[33.8, 43.6]	[37.5, 47.3]	[37.3, 47.2]
Difference between Endometrin and progesterone gel [95% CI lower bound]	-3.6% [-10.3]	0.1% [-6.7]	
Efficacy Population	**(N=392)**	**(N=390)**	**(N=393)**
Pregnancy Rate	156 (40%)	171 (44%)	170 (43%)
95% CI	[34.9, 44.8]	[38.9, 48.9]	[38.3, 48.3]
Difference between Endometrin and progesterone gel [95% CI lower bound]	-3.5% [-10.4]	0.6% [-6.4]	

Abbreviations: BID = twice daily, TID = three times daily, QD = daily, mg = milligrams, CI = confidence interval

Results of the secondary outcome, live birth rate in Trial 2004-02

	Endometrin 100 mg bid	Endometrin 100 mg tid	Progesterone gel qd
ITT Population	**(N=404)**	**(N=404)**	**(N=403)**
Live Birth Rate	141 (35%)	154 (38%)	153 (38%)
95% CI	[30.3, 39.8]	[33.4, 43.1]	[33.2, 42.9]
Difference between Endometrin and progesterone gel 95% CI [95% CI lower bound]	-3.1% [-9.7%]	+0.2% [-6.5%]	
Efficacy Population	**(N=392)**	**(N=390)**	**(N=393)**
Live Birth Rate	141 (36%)	154 (39%)	153 (38%)
95% CI	[31.2, 40.9]	[34.6, 44.5]	[34.1, 43.9]
Difference between Endometrin and progesterone gel 95% CI [95% CI lower bound]	-3.0% [-9.7%]	+0.6% [-6.3%]	

Abbreviations: BID = twice daily, TID = three times daily, QD = daily, mg = milligrams, CI = confidence interval

Results of the secondary outcome, biochemical pregnancy rate in Trial 2004-02

	Endometrin 100 mg bid	Endometrin 100 mg tid	Progesterone gel qd
ITT Population	(N=404)	(N=404)	(N=403)
Pregnancy Rate	198 (49%)	225 (56%)	212 (53%)
95% CI	[44.0, 54.0]	[50.7,60.6]	[47.6, 57.6]
Difference between Endometrin and progesterone gel 95% CI [95% CI lower bound]	-3.6% [-10.5]	3.1% [-3.8]	
Efficacy Population	(N=392)	(N=390)	(N=393)
Pregnancy Rate	198 (51%)	225 (58%)	212 (54%)
95% Confidence Interval	[45.4, 55.6]	[52.6, 62.6]	[48.9, 59.0]
Difference between Endometrin and progesterone gel 95% CI [95% CI lower bound]	-3.4% [-10.4]	3.7% [-3.2]	

The PBAC considered live birth rate per ART cycle to be the most clinically relevant and patient relevant measure of effectiveness of ART, which is consistent with The Assisted Reproduction Technologies Review Committee's Report (2006).

The PBAC noted that the non-inferiority margins used in published ART trials using ongoing pregnancy as the primary endpoints are 6.5 to 10%. The PBAC accepted the non-inferiority limit of -10% proposed by the submission for live births and ongoing pregnancy, in the context of the cost-minimisation proposal.

The PBAC considered the results of the trial supported non-inferiority to progesterone gel, in both twice daily and three times daily doses of Endometrin, with regards to the outcome of live births.

The PBAC considered that Endometrin 100 mg at a dosing frequency of three times daily met the non-inferiority criteria relative to once a day progesterone gel for both ongoing pregnancies and the live birth rate. However, on the basis of the results presented, Endometrin 100 mg twice daily was potentially inferior to progesterone gel 90 mg once daily in terms of ongoing pregnancy, as the lower bound of the 95% confidence interval crosses the pre-specified non-inferiority limit (-10%), but the point estimate of the difference was 3% against Endometrin. Overall, the PBAC considered a conclusion of non-inferiority to be adequately supported by the trial results

A summary of the adverse events in the direct randomised trial (ITT population) is presented below.

Summary of key adverse events in the direct randomised trial (ITT population)

	Endometrin 100 mg bid (N=404)	Endometrin 100 mg tid (N=404)	Progesterone gel qd (N=403)
Subjects with ≥ 1 adverse event	215 (53%)	217 (54%)	210 (52%)
By maximum severity			
Mild	128 (32%)	138 (34%)	141 (35%)
Moderate	71 (18%)	72 (18%)	62 (15%)
Severe	16 (4%)	7 (2%)	7 (2%)
Adverse events by relationship to treatment			
Not related	178 (44%)	174 (43%)	161 (40%)
Uncertain	34 (8%)	38 (9%)	45 (11%)
Probable	3 (1%)	5 (1%)	4 (1%)
Most frequently reported adverse events			
Post –procedural pain	115 (28%)	102 (25%)	102 (25%)
Abdominal pain	43 (11%)	45 (11%)	62 (15%)
Nausea	32 (8%)	29 (7%)	31 (8%)
Ovarian Hyperstimulation	30 (7%)	27 (7%)	26 (6%)
Deaths	0	0	0
Serious Adverse Events	14 (3%)	8 (2%)	9 (2%)
Withdrawals due to Adverse Events	1 (< 1%)	7 (2%)	1 (< 1%)
Adverse drug reactions	3 (1%)	5 (1%)	4 (1%)

Abbreviations: BID = twice daily, TID = three times daily, QD = daily, mg = milligrams

The results for Trial 2004-02 showed a similar adverse event profile between twice daily Endometrin, three times daily Endometrin and progesterone gel once a day. In all three arms of the trial the most frequently reported adverse event was post-procedural pain, which the PBAC considered was likely to be due to other IVF procedures rather than the study drug.

The PBAC also noted in that in all three arms of Trial 2004-02, 1% of participants experienced an adverse event that was likely to be related to the study treatment. A higher proportion of participants in the Endometrin arms (twice and three times daily) than the progesterone gel arm experienced vaginal discharge across all weeks of the trial. The vaginal discharge was likely to be reported as moderate or heavy in the Endometrin three times daily group.

9. Clinical Claim

The submission described Endometrin 100 mg twice daily and Endometrin 100mg three times a day as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over progesterone gel 90 mg once daily.

Overall, the PBAC considered the clinical claim to be adequately supported by the trial results.

10. Economic Analysis

A cost- minimisation analysis was presented in the submission. The equi-effective doses were estimated as Endometrin 100 mg twice daily and three times a day, progesterone gel (90-180 mg once daily) and Oripro progesterone pessaries (200-800 mg daily). The claim that Endometrin 100 mg twice daily and three times a day are equi-effective to progesterone gel 90 mg daily was based on the results from Trial 2004-02. The submission referred to supplementary evidence to support the claim that Endometrin 100 mg twice daily and three times a day are equi-effective to progesterone gel 180 mg daily and Oripro progesterone pessaries (200-800 mg daily).

The PBAC noted that the clinical trial results support the claim that Endometrin 100 mg two or three times daily is equi-effective to progesterone gel 90 mg daily.

The PBAC also noted that Crinone gel supplies 15 applications/days of treatment when used as a single daily dose and 2 packs of Endometrin 100 mg supplies enough for 14 days treatment whether dosed two or three times daily.

11. Estimated PBS Usage and Financial Implications

The likely number of prescriptions dispensed per year was estimated in the submission to be between 10,000 and 50,000 in Year 5. The submission estimated a net nil cost to Government of the requested listing.

The PBAC noted the submission's estimated cost of listing Endometrin was based on substitution of Endometrin for other vaginal preparations across all dosing regimens. Assuming Endometrin only substitutes for progesterone gel 90 mg (once daily) and Oripro pessaries 200 mg once daily, at the price proposed by the submission the net cost to the PBS was underestimated. Revised estimated financial implications resulted in a net cost per year of less than $10 million in Year 5.

12. PBAC Outcome

The PBAC recommended listing of progesterone under the Section 100 IVF/GIFT Program for luteal phase support in patients meeting certain criteria as part of an Assisted Reproductive Technology (ART) treatment program. Listing was recommended on a cost-minimisation basis with progesterone gel (Crinone) taking into account the doses used in the clinical trial, 2004-02, and the number of doses needed to complete a course of treatment.

The PBAC considered that the restriction wording for Endometrin should be consistent with the current restriction wording for progesterone gel (Crinone) and Oripro pessaries.

The PBAC advised that progesterone is not suitable for inclusion in the list of PBS medicines for prescribing by nurse practitioners as Section 100 medicines are currently considered to be out of scope for prescribing by nurse practitioners.

The Safety Net 20 Day Rule should not apply.

The PBAC advised the Minister that under Section 101(3BA) of the *National Health Act 1953*, progesterone should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).

Recommendation:
Recommended

Add new item:

Name, Restriction, Manner of administration and form	Max qty packs	Max. qty units	Proprietary Name and Manufacturer
PROGESTERONE Pessaries, 100 mg, 21	1	21	Endometrin FP

Condition:	Luteal support as part of an assisted reproductive technology (ART) treatment programme for infertile women
Restriction:	Section 100 (IVF/GIFT Treatment)
Clinical criteria:	The treatment must be for luteal phase support; AND Patient must be receiving medical treatment as described in items 13200 or 13201 of the Medicare Benefits Schedule
Definitions	The luteal phase is defined as the time span from embryo transfer until implantation confirmed by positive B-hCG measurement.
Administrative Advice	Supply of these items is through an accredited IVF/GIFT clinic. For enquiries relating to the IVF/GIFT program, medical practitioners should contact Medicare Australia on 1800 700 270.

13. 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.

14. Sponsor's Comment

The sponsor has no comment.