

**5.09 PROGESTERONE,  
200 mg capsule, 42,  
Utrogestan<sup>®</sup>,  
Besins Healthcare Pty Ltd.**

**1 Purpose of Application**

1.1 Section 100 IVF/GIFT program listing for progesterone 200 mg capsule for luteal support as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.

**2 Requested listing**

2.1 The requested restriction is provided below.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PROGESTERONE 200 mg capsule, 42	1	0	\$ [REDACTED]	Utrogestan® Besins Health Care Pty Ltd

<b>Category / Program</b>	Section 100 IVF
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication</b>	Assisted Reproductive Technology
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	The treatment must be for luteal phase support as part of an assisted reproductive technology (ART) treatment cycle for infertile women,  AND  Patient must be receiving medical services as described in items 13200 or 13201 of the Medicare Benefits Schedule.
<b>Definitions</b>	The luteal phase is defined as the time span from embryo transfer until implantation confirmed by positive B-hCG measurement.

2.2 The submission requested listing of micronised progesterone vaginal capsules (hereafter referred to as Utrogestan) 200 mg (three times daily dosing regimen (tid)) based on cost-minimisation to progesterone vaginal gel (Crinone 8%) 90 mg (twice daily dosing regimen (bd)).

### **3 Background**

- 3.1 TGA status: The submission was made under TGA/PBAC parallel process. The Delegate's Overview was received on 2 March 2016. The overview stated that there was no reason, at this time, that the application for Utrogestan should not be approved for registration for use in ART.
- 3.2 Utrogestan had not been considered previously by the PBAC.

### **4 Clinical place for the proposed therapy**

- 4.1 Progesterone is 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. During ART treatment cycles, endogenous progesterone levels may be insufficient due to artificial suppression with GnRH analogues and the luteal phase needs to be supported with exogenous progesterone.
- 4.2 The submission positioned Utrogestan as an alternative to the currently available progesterone therapies for luteal phase support during ART treatment cycles.

### **5 Comparator**

- 5.1 The submission nominated Crinone 8% (90mg) progesterone gel as the comparator. Crinone 8% is an appropriate comparator. The key trial presented in the submission compared Utrogestan 200 mg tid compared with Crinone 8% (90mg) bd, while trials comparing Utrogestan 200 mg tid compared with Crinone 8% (90mg) once daily dosing regimen (qd) were excluded. The submission argued that bd dosing of Crinone 8% is the most widely used in Australian clinical practice and the most stringent efficacy comparison for Utrogestan. However, the submission did not provide any evidence bd dosing of Crinone 8% is any more effective than qd dosing. The sponsor argued that it does not believe there is a requirement to demonstrate the effectiveness of Crinone bd versus qd as the TGA indication and PBS listing support that bd dosing is effective; and the current PBS restriction for Crinone implies that the PBAC has approved its use at a dose of 90 mg qd or bd (PSCR, p.2). The Product Information for Crinone 8% states that "Most women will respond to 90mg given daily" (Crinone Product Information p.8) and the PBAC have previously considered Crinone 8% qd an appropriate comparator (PSD, progesterone (Endometrin), March 2014). The exclusion of the qd dose from consideration was justified in the PSCR (p.2) which stated that a bd dose of Crinone is generally the preference of prescribers and patients. ESC agreed that it is likely that the bd dose would be the most common frequency replaced in practice.
- 5.2 The evaluation and ESC considered that progesterone pessaries may also be appropriate comparators.

**Table 1: Relevant comparators and their respective prices**

Product	Ex-manufacturer price
Crinone 8% progesterone gel	\$ [REDACTED] *
Oripro 100 mg progesterone pessary	\$ [REDACTED]
Oripro 200 mg progesterone pessary	\$ [REDACTED]
Endometrin	\$ [REDACTED]

n.b. Crinone 8% underwent a statutory 5% price reduction on 1 April 2016

\*effective price

Source: Ex-manufacturer prices (excluding Efficient Funding of Chemotherapy) – 1 April 2016.

*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 is based on one head-to-head trial comparing Utrogestan to Crinone (n=430): KAD 93.

6.4 Details of the trial presented in the submission are provided in the table below

**Table 1: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
KAD 93	Efficacy and tolerability of Utrogest 200 vaginal compared with Crinone 8% for luteal phase support during assisted reproduction, Phase III.	Clinical Study Report, 2002
	Jürgen Kleinstein, M.D (2005) Efficacy and tolerability of vaginal progesterone capsules (Utrogest 200) compared with progesterone gel (Crinone 8%) for luteal phase support during assisted reproduction.	<i>Fertility and Sterility</i> 2005; 83 (6); 1641 - 1649

Source: Table B-3 p 35 of the submission, compiled during the evaluation

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

**Table 2: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>Utrogestan 200mg vs Crinone 8% 90mg</b>					
Kleinstein 2005 (KAD 93)	430	R, MC, OL, 12 weeks	Low	Undergoing ART	Ongoing pregnancy at 12 weeks

ART = assisted reproductive therapy MC=multi-centre; OL=open label; R=randomised.

Source: compiled during the evaluation

### Comparative effectiveness

6.6 The submission claimed that there are no clinically meaningful differences between Utrogestan 200 mg three times daily (tid) and Crinone 8% twice daily (bd) with respect to ongoing pregnancies. This was supported by the data from KAD93 as the lower band of the CI for the efficacy population was within the minimal clinically important difference (MCID) (i.e. less than -10%).

**Table 3: Results of ongoing pregnancy at 12 weeks in KAD 93**

	Utrogestan 200 mg tid (N=218)	Crinone 8% 90 mg bd (N=212)
<b>PP Population</b>		
Pregnancy Rate	55 (25.2%)	47 (22.2%)
95% CI	[19.6% - 31.5%]	[16.8% - 28.4%]
Difference between Utrogestan and Crinone 8% [90% CI lower bound]	3.09% [-3.85]	
<b>ITT (Efficacy) Population</b>		
Pregnancy Rate	61 (28%)	57 (26.9%)
95% CI	[22.1% - 34.4%]	[21.0% - 33.4%]
Difference between Utrogestan and Crinone 8% [90% CI lower bound]	1.09% [-6.13%]	

Source: Submission pp 56-57

Abbreviations: PP = per protocol, ITT = intention to treat, CI = confidence interval, tid = three times daily, bd = twice daily

### Comparative harms

6.7 The submission claimed that there are no clinically meaningful differences between Utrogestan 200 mg tid and Crinone 8% bd with respect to adverse events. This was supported by the data presented; however, it should be noted that two of the excluded studies (Simunic 2007 and Ludwig 2002) found significantly more adverse events and tolerability issues were associated with Utrogestan, with the most common of these being vaginal discharge. In addition, Geber (2007, noted that progesterone capsules are associated with more vaginal discharge than vaginal gels. All three studies compared Utrogestan 200 mg tid to Crinone 8% 90 mg once daily (qd).

### Clinical claim

6.8 The submission claimed that Utrogestan 200mg tid is non-inferior to Crinone 8% 90mg bd, in terms of both efficacy and safety. This is reasonable.

6.9 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.10 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

**Economic analysis**

6.11 The equi-effective doses are estimated as Utrogestan 200mg tid (600 mg per day) and Crinone 8% 90mg bd (180 mg per day).

**Table 4: Results of the cost-minimisation analysis**

	Utrogestan 200mg	Crinone 8% 90mg*
Units/course	42	30
Equivalent AEMP/mg	\$ [REDACTED]	\$ [REDACTED]
AEMP/unit	\$ [REDACTED]	\$ [REDACTED]
AEMP/pack	\$ [REDACTED]	\$ [REDACTED]
AEMP/course	\$ [REDACTED]	\$ [REDACTED]

\*effective price

Source: Table D-3, p 96 of the submission

6.12 The sponsor applied a [REDACTED]% discount to Utrogestan to account for the fact that it is likely to substitute, to varying extents, with Crinone and Endometrin at their various TGA approved doses. No further rationale is provided as to why a [REDACTED]% discount would account for substitution with various Crinone and Endometrin doses. The PSCR (p.2) reiterated that the [REDACTED]% discount was appropriate and was applied to allow for uncertainty in the estimated utilisation of other forms of progesterone. ESC noted that the derivation of this figure was unclear. The Pre-PBAC response reiterated that the [REDACTED]% reduction would account for substitution with various progesterone preparations, and was substantial enough to ensure listing of Utrogestan would be cost-neutral to the government.

**Table 5: Requested price of Utrogestan including 19% discount**

	Max qty	DPMQ	AEMP	AEMP/unit	AEMP/mg
Utrogestan (200mg)	42	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

\* effective price

Source: Table D-4, p97 of the submission

6.13 A cost-minimisation analysis between Utrogestan 200 mg tid and Crinone bd is potentially inappropriate in the context that there may be no clinically meaningful difference in efficacy between Crinone 8% 90mg qd and bd. If the PBAC were to recommend Utrogestan for listing on the PBS at a higher price than alternative therapies, the Committee would need to be satisfied that Utrogestan, for some patients, provides a significant improvement in efficacy or reduction in toxicity over the alternative therapies. The alternative therapies in this case include Crinone 8% 90mg qd and the progesterone pessaries. No data is presented to establish superiority or equivalence of Utrogestan over Crinone 8% 90mg qd. The PSCR (p.3)

argued that a cost minimisation against Crinone 90 mg qd is unreasonable for the following reasons: the evaluation accepted that Utrogestan 200 mg tid is non-inferior to Crinone bd, in terms of both efficacy and safety; to the Sponsor's knowledge, neither Oriprio and Endometrin have demonstrated to the PBAC equivalence or superiority over Crinone bd, and clinical expert opinion demonstrated a preference for vaginal progesterone at higher approved doses. ESC considered that Crinone 8% 90mg bd was the appropriate comparator, and that the evidence presented supports the conclusion that Utrogestan tid is non-inferior and that the cost minimisation analysis presented is appropriate.

- 6.14 Presented below is an alternative cost-minimisation analysis conducted during the evaluation which compares Utrogestan 200mg tid to Crinone 8% 90mg qd.

**Table 6: Cost-minimisation analysis assuming equi-effective dose of Utrogestan 200mg TID to Crinone 8% 90mg QD**

	Utrogestan 200mg	Crinone 8% 90mg
mg per day	600 mg	90 mg
Therapeutic relativity	0.15	
Units/pack	42	15
Equivalent AEMP/mg	\$ [REDACTED]	\$ [REDACTED]
AEMP/unit	\$ [REDACTED]	\$ [REDACTED]
AEMP/pack	\$ [REDACTED]	\$ [REDACTED]
AEMP/course	\$ [REDACTED]	\$ [REDACTED]
DPMQ	\$ [REDACTED]	-

Source: calculated during the evaluation

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

- 6.15 The duration of treatment with Utrogestan is 14 days for each ART cycle undertaken. At the submission's cost-minimised price, the cost of Utrogestan/cycle is \$ [REDACTED]. Based on the alternative cost-minimisation analysis calculated during the evaluation, the cost of Utrogestan/cycle is \$ [REDACTED]. As the number of ART cycles a patient will undertake in a year is based on patient preference, estimating the number of cycles a patient will undertake in a year is highly uncertain. The PSCR (p.4) stated that the number of cycles eligible for luteal phase support was based on an analysis of MBS statistics for Medicare item codes 13200 and 13201 and that the sponsor considers this to be the most accurate representation of market size. ESC agreed that this was the best approach to take.

**Estimated PBS usage & financial implications**

- 6.16 This submission was not considered by DUSC. A market share approach was used to derive the financial estimates. Medicare data for MBS item codes 13200 and 13201 was used to estimate the number of cycles for luteal phase support because there was limited S100 IVF utilisation data available. The submission assumed that the listing of Utrogestan would not grow the overall progesterone market but estimated there to be a net cost of less than \$10 million to the PBS over the first five years of listing. The estimated cost to the PBS based on the requested price is dependent on the extent to which Utrogestan displaces other forms of progesterone. The pre-PBAC response stated that it is reasonable to expect some impact, albeit a small impact, on the PBS budget, dependent on the extent to which Utrogestan displaces other forms of progesterone.

- 6.17 The submission may have overestimated the expected increase in the overall progesterone market over the first five years of listing by using a linear extrapolation of number of Medicare items processed in 2011 to 2014. However, the requested listing of Utrogestan is not expected to increase the market, in any case. The pre-PBAC response reiterated that this market uptake is an ambitious assumption, and as such, mitigates any risk to the PBAC of potentially underestimating the uptake of Utrogestan.
- 6.18 In addition, the submission overestimated the uptake of Utrogestan of the total market by multiplying the assumed uptake rates for each of the three types of progesterone by the total market instead of the individual market shares. After revising the usage estimates during the evaluation, the net impact on the PBS is a save of less than \$10 million over the first five years of listing. The financial impact using the alternative cost minimised price was also calculated during the evaluation. At a DPMQ of \$██████, there is estimated to be a net save of less than \$10 million to the PBS over the first five years of listing.

**Table 7: Estimated use and financial implications<sup>a</sup>**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Estimated number of patient cycles treated with progesterone	██████	██████	██████	██████	██████
Utrogestan market share	7%	14%	20%	25%	28%
Utrogestan scripts <sup>b</sup>	██████	██████	██████	██████	██████
<b>Estimated net cost to PBS</b>					
Increased utilisation of Utrogestan	\$██████	\$██████	\$██████	\$██████	\$██████
Reduced utilisation of other drugs	\$██████	\$██████	\$██████	\$██████	\$██████
Net cost to other Government Health Budgets	\$0	\$0	\$0	\$0	\$0
<b>Net cost to PBS/RPBS/MBS</b>	\$██████	-\$██████	-\$██████	-\$██████	-\$██████
<b>Net cost to PBS/RPBS/MBS using DPMQ of \$84.92</b>	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████

<sup>a</sup> Figures in italics reflect the revised usage estimates calculated during the evaluation (see Section E(i) 2(cma) for further details).

<sup>b</sup> Assuming 1 pack per IVF cycle as estimated by the submission

Source: Utrogestan Section E workbook and calculated during the evaluation

The redacted table shows that at year 5, the estimated number of patient cycles treated with progesterone is 10,000 – 50,000, and the estimated number of Utrogestan prescriptions is 10,000 – 50,000.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

## 7 PBAC Outcome

- 7.1 The PBAC decided not to recommend progesterone 200 mg capsule (Utrogestan) for PBS listing on the basis that the cost-minimisation analysis was not conducted against the appropriate comparator.
- 7.2 The PBAC considered that any form of progesterone currently listed on the PBS for ART could be an appropriate comparator. At the time of PBAC consideration, progesterone pessary and progesterone 8% vaginal gel were listed on the PBS. The PBAC noted that progesterone pessary was the lowest priced of these comparators. The PBAC advised that in the absence of demonstrated superior comparative effectiveness or comparative safety over the least costly comparator, progesterone 200 mg capsule should be cost-minimised to the least costly comparator, progesterone pessary.
- 7.3 The PBAC noted the head-to-head trial of progesterone 200 mg capsule vs progesterone 8% vaginal gel (KAD 93) and accepted that the data supported a claim of non-inferiority in terms of clinical effectiveness and safety between progesterone 200 mg capsule and progesterone 8% vaginal gel.
- 7.4 As the submission did not provide evidence that progesterone 200 mg capsule provides a significant improvement in efficacy or reduction of toxicity over progesterone pessary for some patients, the PBAC considered there was no basis for progesterone to have a price advantage over progesterone pessary for an equivalent treatment period.
- 7.5 The PBAC considered that the arbitrary ■% discount offered by the sponsor did not sufficiently take into account the fact that progesterone 200 mg capsule would substitute, in some instances, to the significantly cheaper progesterone pessary.
- 7.6 The PBAC noted that the sponsor may wish pursue listing via a minor submission including a clinical comparison and/or cost-minimisation analysis between progesterone 200 mg capsule and progesterone pessary.
- 7.7 The PBAC noted that this submission is eligible for an Independent Review

### **Outcome:**

Rejected

## 8 Context for Decision

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

**9 Sponsor's Comment**

The sponsor is disappointed but remains committed to working with the PBAC and Department of Health to ensure that Utrogestan is made available to infertile women for luteal phase support as part of an Assisted Reproductive Technology program.