

7.05 PROGESTERONE, capsule, 200 mg, Utrogestan[®], Besins Healthcare Pty Ltd.

1 Purpose of Application

- 1.1 The minor submission requested a Section 100 IVF listing for progesterone for luteal support as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.

2 Requested listing

- 2.1 The minor submission proposed a revised DPMQ, for micronised progesterone vaginal capsules (hereafter referred to as Utrogestan) 200 mg (three times daily dosing regimen (tds)) for the same restriction as in the March 2016 major submission as follows.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
PROGESTERONE 200 mg capsule, 42	1	0	\$ [REDACTED]	Utrogestan®	Besins Health Care Pty Ltd
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				
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 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.				
Definitions	The luteal phase is defined as the time span from embryo transfer until implantation confirmed by positive B-hCG measurement.				

3 Background

- 3.1 At the time of the PBAC meeting, Utrogestan did not have TGA marketing approval. At its 309th meeting on 1st April 2016, the ACPM considered that Utrogestan had an overall positive benefit-risk profile for the indication of “luteal support of assisted reproductive technology”.

- 3.2 Utrogestan was previously considered by the PBAC at the March 2016 meeting. 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.

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

4 Clinical place for the proposed therapy

- 4.1 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. During ART treatment cycles, endogenous progesterone levels may be insufficient 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.

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

5 Comparator

- 5.1 The minor submission nominated a mixed comparator comprising all PBS listed vaginal formulations and TGA approved doses. Previously, the sponsor nominated Crinone 8% (90 mg) progesterone gel as the comparator [March 2016 PBAC meeting]. 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.
- 5.2 In accordance with the *National Health Act 1953*, Section 101(3B), "where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal preparations, is substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the PBAC: (a) shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the PBAC is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies".
- 5.3 The minor submission addressed the PBAC's recommendation from the March 2016 meeting by arguing that a mixed comparator approach was justified on the basis of differences in tolerability between the available vaginal progesterone presentations and patients' and prescribers' preferences for one product over another.

- 5.4 The PBAC did not accept the minor submission's arguments and maintained its view that progesterone pessary is the appropriate comparator.
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 as it was a minor submission.

Consumer comments

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

Clinical trials

- 6.3 No new clinical trials were presented in the submission.
- 6.4 The submission presented a comparison of the adverse effect profiles documented in the Product Information of Oriprio and Endometrin pessaries and Crinone gel to assert that those products are associated with unpleasant local side effects (vaginal irritation or messy vaginal discharge, respectively), which may limit patient acceptability. By contrast, the results of two company-sponsored studies enrolling 452 women demonstrated that overall, Utrogestan is well tolerated. In the pivotal study (Clinical Study Report, 2002), three single cases of AEs were considered to be definitely related to Utrogestan: local discomfort, bloating, and vaginal discharge. Kleinstein (2005) reported that "Tolerability of both drugs was good and very few study drug-related adverse events were observed in both groups" but that "Occasionally observed local irritation or discomfort caused by (cloddy) disposal or discharge of drug material may have contributed to the comparatively worse rating of Crinone 8% gel overall tolerability and acceptance by patients and physicians". On the basis of these data, the Utrogestan Draft Product Information (2015) states that "no major local intolerance issues have been reported during the different clinical trials of Utrogestan, even if some burning, pruritus or fatty discharge have been observed and reported in the literature; incidences were extremely low".
- 6.5 The PBAC considered that Utrogestan did not provide a significant improvement in efficacy or reduction of toxicity compared to, progesterone pessary.

Clinical claim

- 6.6 The PBAC considered that the claim of non-inferior comparative effectiveness and non-inferior comparative safety was reasonable.

Economic analysis

- 6.7 In the previous major submission considered by PBAC in March 2016, the submission presented a cost-minimisation analysis against Crinone 8% (90 mg) progesterone gel. The PBAC considered that progesterone gel was not the appropriate comparator and advised that Utrogestan should be cost-minimised to the least costly comparator, progesterone pessary.

- 6.8 The minor submission presented a cost-minimisation analysis using the therapeutic relativities and relative utilisation weightings of all PBS-listed progesterone products at their various TGA approved doses. The relative utilisation weightings were based on three sources: a 10% longitudinal sample of prescription data from the Department of Human Services (base case); primary market research from six fertility specialists (sensitivity analysis 1); and therapeutic relativities previously accepted by the PBAC (sensitivity analysis 2). Results of the cost-minimisation analyses are presented in Table 1.

Table 1: Cost minimisation analyses

Comparator price					Relative utilisation		
Comparator	Dose	Therapeutic relativity	AEMP/mg	EE AEMP/mg	Base case ^a	SA 1 ^b	SA 2 ^c
Crinone 8% (90 mg) gel	90 mg daily	0.15	\$ [REDACTED]	\$ [REDACTED]	9%	21%	63%
	90 mg bd	0.30	\$ [REDACTED]	\$ [REDACTED]	54%	42%	0%
Oriprio 200 mg pessary	200 mg daily	0.33	\$ [REDACTED]	\$ [REDACTED]	1%	5%	21%
	200 mg bd	0.67	\$ [REDACTED]	\$ [REDACTED]	20%	16%	0%
	400 mg bd	1.33	\$ [REDACTED]	\$ [REDACTED]	0%	0%	0%
Oriprio 100 mg pessary	100 mg bd	0.33	\$ [REDACTED]	\$ [REDACTED]	1%	1%	1%
Endometrin 100 mg pessary	100 mg tds	0.50	\$ [REDACTED]	\$ [REDACTED]	13%	11%	13%
	100 mg bd	0.33	\$ [REDACTED]	\$ [REDACTED]	3%	5%	3%
Utrogestan price	Dose	Max qty	AEMP/unit	EE AEMP/mg	AEMP		
Base case	Utrogestan 200 mg tds	42	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]		
SA 1		42	\$ [REDACTED]	\$ [REDACTED]		\$ [REDACTED]	
SA 2		42	\$ [REDACTED]	\$ [REDACTED]			\$ [REDACTED]

^a Base case: 10% longitudinal sample of prescription data from the Department of Human Services

^b SA 1: 10% longitudinal sample of prescription data from the Department of Human Services

^c SA 2: therapeutic relativities previously accepted by the PBAC

Abbreviations: bd=twice daily; EE=equi-effective; SA=sensitivity analysis; tds=three times daily

Source: Table 6 p12, Table 8 p13 and Table 9 p14 of the submission

- 6.9 The submission requested an AEMP of \$ [REDACTED] for Utrogestan 200 mg capsule, 42. The pre-PBAC response clarified that this AEMP was proposed on the basis of the prices calculated in the base case and sensitivity analysis 1, and argued that this AEMP, “compares very favourably with the AEMP per course of other progesterone formulations”
- 6.10 The therapeutic relativities used by the submission were based on the relativity of Utrogestan 200 mg three times a day versus all TGA-approved doses of all PBS-listed progesterone products. No clinical evidence was provided to demonstrate the superiority of higher progesterone doses over lower doses. On this basis, the inclusion of higher prices for the higher progesterone doses in deriving a weighted price for Utrogestan may not be justified.

6.11 The previously accepted equi-effective doses by PBAC are presented in Table 2.

Table 2: Established equi-effective doses accepted by the PBAC

Item	PBAC meeting	Comparator	Equi-effective doses	Source
Crinone 8% (90 mg) vaginal gel	Dec 2002	Non-PBS pessary	Crinone gel 90 mg per dose = progesterone pessary 200 mg per dose	Therapeutic relativity sheet
Oripro pessary, 100 mg, 200 mg	Dec 2003	Crinone gel	Crinone gel 90 mg/day = Oripro 200 mg/day	
Endometrin vaginal tablet, 100 mg	Mar 2014	Crinone gel + Oripro pessary (100 mg, 200 mg)	Endometrin 100 mg bd or tds = Crinone 90-180 mg daily = Oripro 200-800 mg daily	Endometrin PSD March 2014

Drug cost/cycle: \$ [REDACTED]

6.12 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]. 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.

Estimated PBS usage & financial implications

6.13 A market share approach was used to derive the financial estimates. The minor submission assumed that the listing of Utrogestan would not grow the overall progesterone market, and estimated a net save to the PBS of less than \$10 million in Year 5 of listing, with a total net save to the PBS of less than \$10 million over the first 5 years of listing. The estimated financial impact to the PBS is dependent on the extent to which Utrogestan displaces other forms of progesterone. The submission assumed Crinone 8% gel as the product most likely to be displaced by Utrogestan: by Year 5, the proportion of total market displaced by Utrogestan is estimated at 50%, with 40% displacing Crinone 8% gel and 5% displacing each of Oripro and Endometrin. Given that Crinone 8% gel is the most costly product, the assumption that it is the most displaced product may overestimate the projected net save to the PBS. As Utrogestan is a capsule formulation, it may be more likely to displace greater proportions of the Oripro and Endometrin (pessary) market rather than Crinone 8% gel. On this basis, the estimated net saving to the PBS is uncertain.

6.14 This estimated extent of use of Utrogestan and cost to the PBS is presented in Table 3.

Table 3: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Estimated extent of use						
Estimated number of patient cycles treated with progesterone	██████	██████	██████	██████	██████	██████
Utrogestan market share	15%	25%	35%	45%	50%	NA
Utrogestan scripts	██████	██████	██████	██████	██████	██████
Estimated net cost to PBS/RPBS						
Increased utilisation of Utrogestan	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Reduced utilisation of other drugs	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Net cost to other Government health budgets	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████

Source: Utrogestan Section E workbook (Excel) provided in the electronic submission

The redacted table shows that at year 5, the estimated number of patients would be 10,000 – 50,000 per year, and the net save to the PBS would be less than \$10 million per year.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 100 IVF (Streamlined) listing for progesterone for luteal support as part of an Assisted Reproductive Technology (ART) treatment program for infertile women. The PBAC considered that any form of progesterone currently listed on the PBS for ART could be an appropriate comparator, and that in the absence of demonstrated superior comparative effectiveness or safety over the least costly comparator, progesterone 200 mg capsule should be cost-minimised to the least costly comparator, progesterone pessary.
- 7.2 The PBAC considered that the equi-effective doses were progesterone (Utrogestan) 200 mg capsule administered vaginally three times daily and the previously accepted progesterone equi-effective doses, which are Oripio pessary 200-800 mg daily and Endometrin vaginal tablet 100 mg twice or three times daily (refer to Table 2). The PBAC noted that no clinical evidence was provided to demonstrate the superiority of higher progesterone doses over lower doses.
- 7.3 The PBAC did not accept the submission’s mixed comparator approach, as the PBAC was not satisfied that progesterone (Utrogestan) was of superior comparative effectiveness or safety over the least costly comparator, progesterone pessary. The PBAC noted the submission’s claim of differences in tolerability between the available vaginal progesterone presentations and patients’ and prescribers’ preferences for one product over another. However, in the absence of demonstrated clinical trial evidence that progesterone (Utrogestan) provided a significant improvement in efficacy or reduction of toxicity compared to the least costly

comparator, progesterone pessary, the PBAC advised that a price advantage for progesterone (Utrogestan) was not justified.

- 7.4 The PBAC considered that the projected savings to the PBS as proposed by the submission was likely overestimated, given that the submission assumed that Crinone 8% gel was the product most likely to be displaced by progesterone (Utrogestan).
- 7.5 The PBAC advised that progesterone is not suitable for prescribing by nurse practitioners.
- 7.6 The PBAC recommended that the Early Supply Rule should not apply.
- 7.7 The PBAC noted that this submission is not eligible for an Independent Review given that the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
PROGESTERONE 200 mg capsule, 42	1	0	Utrogestan®	Besins Health Care Pty Ltd

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
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 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.
Definitions	The luteal phase is defined as the time span from embryo transfer until implantation confirmed by positive B-hCG measurement.

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

The sponsor had no comment.