

5.10 PROGESTERONE, Pessary 400 mg, Cyclogest, Gedeon Richter Australia Pty Ltd.

1 Purpose of submission

- 1.1 This Category 2 submission requested a PBS Section 100 - IVF Program Authority Required (STREAMLINED) listing for 400 mg progesterone vaginal pessary (Cyclogest®) for the treatment of infertile women who require luteal phase support as part of an Assisted Reproductive Technology (ART) treatment cycle.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus Crinone® as the main comparator, with Utrogestan® and Endometrin® as secondary comparators. Utrogestan was used in the cost-minimisation analysis because it is the lowest cost of all the progesterone brands currently listed on the PBS.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Infertile women who need luteal phase support as a part of the assisted reproductive technology (ART) therapy.
Intervention	400 mg progesterone vaginal pessaries (Cyclogest) BID
Comparator	Primary comparator: <ul style="list-style-type: none"> • Crinone 8% (90 mg) progesterone vaginal gel QD or BID Supplementary comparators: <ul style="list-style-type: none"> • Utrogestan 200 mg micronised progesterone vaginal capsule TID • Endometrin 100 mg micronised progesterone vaginal pessary BID or TID
Outcomes	<ul style="list-style-type: none"> • Clinical pregnancy • Ongoing pregnancy • Biochemical pregnancy
Clinical claim	Cyclogest is non-inferior to Crinone, Utrogestan and Endometrin in terms of clinical efficacy Cyclogest is non-inferior to Crinone, Utrogestan and Endometrin in terms of safety

Source: Table 1.1.1, p4 of the submission.

Abbreviations: ART = Assisted Reproductive Technology; BID = Twice daily; PBS = Pharmaceutical Benefits Scheme; QD = Once daily; TID = Three times daily

2 Background

Registration status

- 2.1 Cyclogest was TGA registered on 11 February 2022. The product was registered in the United Kingdom (November 2015), the European Union (January 2017 via the decentralised procedure) and in other countries.
- 2.2 The approved indication for Cyclogest is “for luteal phase support as a part of an Assisted Reproductive Technology (ART) treatment for women”, which is consistent with the PBS restriction.

Previous PBAC consideration

2.3 This is the first submission to the PBAC for Cyclogest. There are four progesterone brands currently listed on the PBS for luteal phase support as part of an ART treatment cycle for infertile women: Crinone, Oriprio[®], Endometrin and Utrogestan.

3 Requested listing

3.1 Suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
PROGESTERONE					
progesterone 400 mg pessary, 15	NEW	2	30	0	Cyclogest
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: Section 100 – IVF Program					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [4997]					
Administrative Advice: <i>No increase in the maximum quantity or number of units may be authorised.</i>					
Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>					
Indication: Assisted Reproductive Technology					
Clinical criteria:					
The treatment must be for luteal phase support as part of an assisted reproductive technology (ART) treatment cycle for infertile women					
AND					
Clinical criteria:					
Patients must be receiving medical services as described in items 13200 or 13201 of the Medicare Benefits Schedule					
Prescribing Instructions: The luteal phase is defined as the time span from embryo transfer until implantation confirmed by positive B-hCG measurement					

3.2 The submission requested the listing and restrictions for Cyclogest be the same as other progesterone preparations currently PBS-listed for this indication. The PBAC considered this to be appropriate.

3.3 The submission requested a maximum quantity of 30 units with nil repeats. The submission proposed that Cyclogest be initiated at embryo transfer and be restricted to luteal phase support (approximately 2 weeks of treatment), consistent with other listings for progesterone for luteal phase support, with the exception of Oriprio pessary 200 mg, which has a maximum quantity of 45 units, which provides treatment for approximately 11 days when used at the maximum recommended dose (400 mg twice a day), and Oriprio pessary 100 mg which has a maximum quantity of 45 units, which provides treatment for approximately 5.5 days when used at the maximum

recommended dose. The PBAC noted that the TGA's ACM was of the view that the proposed treatment duration should be continued until 12 weeks of gestation; that is "If pregnancy has been confirmed, the administration of progesterone should be continued for 38 days from the start of therapy or up until 12 weeks of pregnancy according to need at the judgement of the treating physician." (Cyclogest ACM minutes). The PBAC considered the maximum quantity and repeats to be appropriate for the treatment of luteal phase support and aligned with the TGA approved product information for Cyclogest.

- 3.4 The PBAC noted that under the Section 100 IVF medicines policy, repeats are not permissible for these medicines however prescribers may request prior approval to prescribe additional quantity if a patient requires a quantity beyond the PBS listed maximum quantity. Therefore, the PBAC advised the following administrative advice regarding maximum repeats be added to the Cyclogest restriction and this should flow-on to all medicines listed under the Section 100 IVF program "No increase in the maximum number of repeats may be authorised".
- 3.5 The submission proposed no special pricing arrangement for Cyclogest.

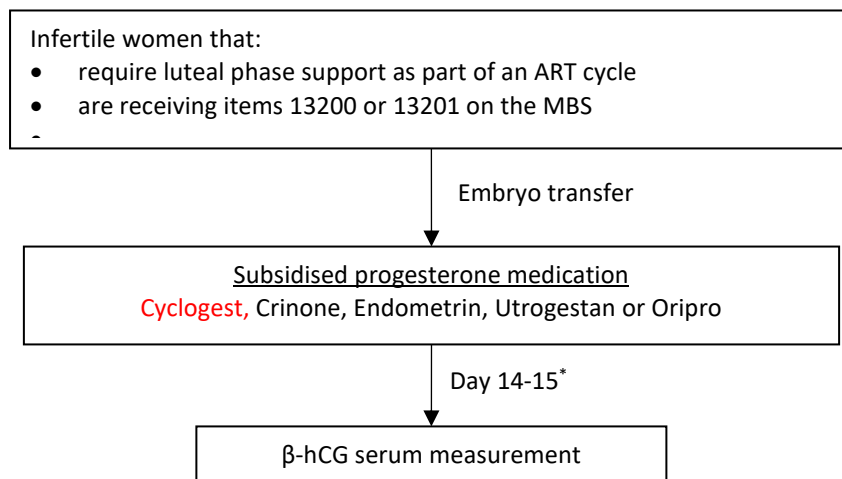
For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Infertility, defined as the failure to achieve pregnancy after 12 months or more of regular unprotected intercourse, impacts one in six Australians.
- 4.2 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 due to artificial suppression with GnRH analogues and the luteal phase needs to be supported with exogenous progesterone.
- 4.3 The submission positioned Cyclogest as an alternative progesterone to the currently available progesterone therapies for luteal phase support during ART treatment cycles, which include Crinone 8% (90 mg) (vaginal gel) once daily (QD) or twice daily (BID), Utrogestan 200 mg (vaginal capsule) three times daily (TID), Endometrin 100 mg (vaginal pessary) BID/TID, and Oriprio 100 mg or 200 mg (vaginal pessary) (200 mg daily up to a maximum of 400mg BID, Oriprio PI).
- 4.4 The PBS restrictions for progesterone medicines define the luteal phase as '...the time span from embryo transfer until implantation confirmed by a positive β -hCG measurement', which is typically assessed 2 weeks after embryo transfer. The requested listing for Cyclogest was consistent with the treatment duration of 2 weeks,

however, shorter than the treatment duration in the key clinical trial. Further discussion is included below in Section 6 ‘Clinical trials’.

Figure 1: Proposed treatment algorithm with Cyclogest as another progesterone product for luteal phase support



Source: Figure 1.2-1, p31 of the submission.

Abbreviations: ART = Assisted Reproductive Technology; hCG = human chorionic gonadotropin; MBS = Medicare Benefits Schedule

* The maximum quantity for alternative progesterone brands of Endometrin, Utrogestan and Oriprio is 14-15 days or slightly longer. However, the maximum quantity for Crinone (2 packs, 15 application each) is sufficient to up to 4 weeks of treatment if used once daily.

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

5 Comparator

- 5.1 The submission nominated Crinone 8% (90 mg) progesterone vaginal gel (hereafter Crinone) QD/BID as the main comparator. The main argument provided in support of this nomination was that Crinone currently has the largest market share amongst all other PBS progesterone brands for the same target population. The evaluation comparative clinical efficacy and safety of Cyclogest versus Crinone was established directly through a head-to-head RCT comparing Cyclogest 400 mg BID and Crinone 8% (90 mg) QD.
- 5.2 The submission identified Utrogestan 200 mg micronised progesterone vaginal capsules TID and Endometrin 100 mg micronised progesterone vaginal pessaries BID/TID as supplementary comparators on the basis that they are alternative progesterone brands on the PBS for the same target population. The comparative clinical efficacy and safety of Cyclogest versus Utrogestan/Endometrin were established using indirect comparisons with Crinone as a common comparator. There were no direct RCTs of Cyclogest versus Utrogestan/Endometrin for efficacy. This information was relevant for identifying relevant alternative therapies as per Section 101(3B) of the *National Health Act 1953*.

- 5.3 The submission excluded both Oriprio 100 mg and Oriprio 200 mg because there was no clinical evidence available to compare Cyclogest and Oriprio for luteal phase support as a part of ART cycle. This was appropriate.
- 5.4 The PBAC considered the nominated comparator Crinone to be appropriate. The PBAC noted there are no trials or studies of Cyclogest BID versus Crinone BID. The PBAC also noted there is a lack of data to demonstrate the superiority of higher progesterone doses over lower dose and that clinicians would determine the best treatment regimens based on their patients' needs. The PBAC also noted the therapeutic relativities used by the submission were based on the relativity of Cyclogest versus all TGA-approved doses of all PBS-listed progesterone products which was reasonable.

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 one phase 3, multicenter, head-to-head, open-label, randomised (1:1), non-inferiority clinical efficacy, safety and tolerability trial comparing Cyclogest 400 mg progesterone vaginal pessaries BID to Crinone 8% (90 mg) progesterone vaginal gel QD in 769 women aged 18-40 years.
- 6.4 The submission also presented two supplementary indirect comparisons of Cyclogest BID: to Utrogestan TID via four RCTs comparing Utrogestan and Crinone QD (Michnova et al. 2017, Ganesh et al. 2011, Geber et al. 2007, Simunic et al. 2007)¹ and one RCT comparing Utrogestan BID with Crinone BID (KAD 93 - Kleinstein, 2005)², and to Endometrin 100 mg progesterone vaginal tablets BID via one RCT comparing

¹ MICHNOVA, L., DOSTAL, J., KUDELA, M., HAMAL, P. & LANGOVA, K. 2017. Vaginal use of micronized progesterone for luteal support. A randomized study comparing Utrogestan® and Crinone® 8. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*, 161, 86-91.

GANESH, A., CHAKRAVORTY, N., MUKHERJEE, R., GOSWAMI, S., CHAUDHURY, K. & CHAKRAVARTY, B. 2011. Comparison of oral dydrogesterone with progesterone gel and micronized progesterone for luteal support in 1,373 women undergoing in vitro fertilization: a randomized clinical study. *Fertil Steril*, 95, 1961-5.

GEBER, S., MOREIRA, A. C., DE PAULA, S. O. & SAMPAIO, M. 2007. Comparison between two forms of vaginally administered progesterone for luteal phase support in assisted reproduction cycles. *Reprod Biomed Online*, 14, 155-8

SIMUNIC, V., TOMIC, V., TOMIC, J. & NIZIC, D. 2007. Comparative study of the efficacy and tolerability of two vaginal progesterone formulations, Crinone 8% gel and Utrogestan capsules, used for luteal support. *Fertil Steril*, 87, 83-7.

² KLEINSTEIN, J. 2005. Efficacy and tolerability of vaginal progesterone capsules (Utrogest 200) compared with progesterone gel (Crinone 8%) for luteal phase support during assisted reproduction. *Fertil Steril*, 83, 1641-9

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Endometrin with Crinone (2004-02)³, and one RCT comparing the side effects of Endometrin with Cyclogest after 14 days of treatment (Ng et al 2007)⁴.

6.5 The trials presented in the submission are summarised in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ACT-CYC-300-2013-01	<p><u>Clinical study report</u> Randomised Clinical Trial to Compare the Pregnancy Rates of Vaginally Applied Cyclogest Pessary and Crinone 8% Gel After In-vitro Fertilization. Approval Date: 10 December 2014</p> <p><u>Publication</u> Saunders, H., Khan, C., D'hooghe, T., Magnusdottir, T. B., Klingmann, I., Hrafnisdottir, S. & Vaginal Progesterone Luteal Phase Support Post, I. V. F. S. G. 2020. Efficacy, safety and tolerability of progesterone vaginal pessaries versus progesterone vaginal gel for luteal phase support after in vitro fertilisation: a randomised controlled trial. Hum Reprod, 35, 355-363.</p> <p>EudraCT 2013-001105-81</p>	<p>Clinical Study Report, December 2014</p> <p>Saunders et al 2020</p>
Michnova et al 2017	<p><u>Publication</u> Michnova, L., Dostal, J., Kudela, M., Hamal, P. & Langova, K. 2017. Vaginal use of micronized progesterone for luteal support. A randomised study comparing Utrogestan and Crinone 8. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub, 161, 86-91.</p>	Michnova et al 2017
Ganesh et al 2011	<p><u>Publication</u> Ganesh, A., Chakravorty, N., Mukherjee, R., Goswami, S., Chaudhury, K. & Chakravarty, B. 2011. Comparison of oral dydrogesterone with progesterone gel and micronized progesterone for luteal support in 1,373 women undergoing in vitro fertilization: a randomized clinical study. Fertil Steril, 95, 1961-5</p>	Ganesh et al 2011
Geber et al. 2007	<p><u>Publication</u> Geber, S., Moreira, A. C., De Paula, S. O. & Sampaio, M. 2007. Comparison between two forms of vaginally administered progesterone for luteal phase support in assisted reproduction cycles. Reprod Biomed Online, 14, 155-8.</p>	Geber et al 2007
Simunic et al 2007	<p><u>Publication</u> Simunic, V., Tomic, V., Tomic, J. & Nizic, D. 2007. Comparative study of the efficacy and tolerability of two vaginal progesterone formulations, Crinone 8% gel and Utrogestan capsules, used for luteal support. Fertil Steril, 87, 83-7.</p>	Simunic et al 2007
KAD 93	<p><u>Publication</u> Kleinstein, J. 2005. Efficacy and tolerability of vaginal progesterone capsules (Utrogest 200) compared with progesterone gel (Crinone 8%) for luteal phase support during assisted reproduction. Fertil Steril, 83, 1641-9.</p>	Kleinstein et al 2005
2004-02	<p><u>Publication</u></p>	Doody et al 2009

³ DOODY, K. J., SCHNELL, V. L., FOULK, R. A., MILLER, C. E., KOLB, B. A., BLAKE, E. J. & YANKOV, V. I. 2009. Endometrin for luteal phase support in a randomised, controlled, open-label, prospective in-vitro fertilization trial using a combination of Menopur and Bravelle for controlled ovarian hyperstimulation. Fertil Steril, 91, 1012-7.

⁴ NG, E. H., CHAN, C. C., TANG, O. S. & HO, P. C. 2007. A randomised comparison of side effects and patient convenience between Cyclogest suppositories and Endometrin tablets used for luteal phase support in IVF treatment. Eur J Obstet Gynecol Reprod Biol, 131, 182-8.

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Trial ID	Protocol title/ Publication title	Publication citation
	Doody, K. J., Schnell, V. L., Foulk, R. A., Miller, C. E., Kolb, B. A., Blake, E. J. & Yankov, V. I. 2009. Endometrin for luteal phase support in a randomised, controlled, open-label, prospective in-vitro fertilization trial using a combination of Menopur and Bravelle for controlled ovarian hyperstimulation. <i>Fertil Steril</i> , 91, 1012-7. Clinicaltrials.gov: NCT00296478 (no results available)	
Ng et al 2007	Publication Ng, E. H., Chan, C. C., Tang, O. S. & Ho, P. C. 2007. A randomised comparison of side effects and patient convenience between Cyclogest suppositories and Endometrin tablets used for luteal phase support in IVF treatment. <i>Eur J Obstet Gynecol Reprod Biol</i> , 131, 182-8.	Ng et al 2007

Source: Table 2.2.2. p27, Table 2(a)2.2. p69 of the submission and Table 2(b)2.2. p21 of Appendix 1 of the submission.

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

Table 3: Key features of included trials

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes
Cyclogest 400 mg BID versus Crinone 8% (90 mg) QD					
ACT-CYC-300-2013-01	769	R, OL 70 days after OR	High	Infertile women who need LPS for ART cycles	<ul style="list-style-type: none"> Clinical pregnancy rate (foetal heart movement examined by TVUS) at 38 days after oocyte retrieval (OR) Clinical pregnancy rate at 70 days after OR Biochemical pregnancy rate (serum β-hCG concentration >25 IU/L) at 18 and 38 days after OR Clinical implantation rate at 38 and 70 days after OR Patient's evaluation of treatment convenience Patient's evaluation of bleeding and leakage (diary)
Utrogestan 200 mg TID versus Crinone 8% (90 mg) QD – for the indirect comparison of Cyclogest versus Utrogestan					
Michnova et al 2017	111	R 10 weeks after OR	Medium to High	Women aged 18-40 years undergoing IVF/ET	<ul style="list-style-type: none"> Pregnancy based on positive blood test Clinical pregnancy Ongoing pregnancy at or later than week 12 of pregnancy Ongoing pregnancy at or later than week 20 of pregnancy Birth rate
Ganesh et al 2011	1,363	R Single blinded 12 weeks of pregnancy	Medium to High	Infertile women (aged 23 to 42 years) who underwent controlled ovarian stimulation for IVF treatment (fresh cycle).	<ul style="list-style-type: none"> Clinical pregnancy rate at week 7 (after ET) Miscarriage rate

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Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes
Cyclogest 400 mg BID versus Crinone 8% (90 mg) QD					
Geber et al 2007	244	R 12 weeks of pregnancy (approx. 10 weeks from OR)	Medium to High	Women who underwent controlled ovarian stimulation for IVF treatment (fresh cycle).	<ul style="list-style-type: none"> Clinical pregnancy rate at week 2-4 weeks after OR (equivalent to 4-6 weeks after ET) Miscarriage rate
Simunic et al 2007	285	R 12 weeks of pregnancy	Medium to High	Women aged <37 who underwent an IVF or ICSI cycle of ART	<ul style="list-style-type: none"> Clinical pregnancy rate at 4-6 weeks after ET Patient reported ease of administration, convenience of use, and preference
KAD 93	430	R, OL Up to gestational week 12 (approx. 10 weeks of treatment) Crinone 8% (90 mg), BID	Medium to High	Women (age ≥18 and ≤35 years) who had IVF-ICSI and presented for their first ART cycle	<ul style="list-style-type: none"> Ongoing pregnancy rate at the end of week 12 Implantation rate Abortion rate Rate of withdrawals
Endometrin versus Crinone – for the indirect efficacy comparison Cyclogest versus Endometrin					
2004-02	1,211	R, OL 10 weeks after OR (approx. 12 weeks of gestation)	Medium	Infertile women aged 18-42 years who required IVF	<ul style="list-style-type: none"> Clinical pregnancy rate (identification of foetal heart movement) at approx. 6 weeks after ET Biochemical pregnancy rate (positive β-hCG pregnancy test) at Day 12-14 after ET Clinical pregnancy rate (presence of a gestational sac on ultrasound examination) at 4 weeks after ET Live birth rate
Endometrin versus Cyclogest – for the safety comparison					
Ng et al 2007	132	R, 14 days from embryo transfer.	High	Infertile women undergoing IVF/ICSI	<ul style="list-style-type: none"> Perineal irritation Side effects Patient inconvenience Clinical pregnancy rate (presence of one or more gestational sac)

Source: Table 2.3.1 p31, Table 2(a).3.1 pp73-75, Table 2(a).4.2 p91 of the submission; Table 2(b).3.2 pp9-10, Table 2(b).4.1 p17 and Table 2(b).4.2 p20 in Appendix 1 of the submission; ACT-CYC-300-2013-01 CSR p40-41 and p660; Saunders et al. (2020) p357; Michnova et al. (2017); Ganesh et al. (2011); Geber et al. (2007); Simunic et al. (2007); KAD 93 (Kleinstein et al., 2005); 2004-02 (Doody et al., 2009); Ng et al. (2007).

Abbreviations: β-hCG: Beta Human Chorionic Gonadotropin; ET: Embryo transfer, ICSI: Intracytoplasmic sperm injection, IVF: In vitro fertilization, NA: not applicable, OL: open-label, OR: oocyte retrieval, R: randomised

6.7 The key trial ACT-CYC-300-2013-01 comparing Cyclogest BID to Crinone QD was designed as a non-inferiority trial with an initial non-inferiority margin of -9% in the proportion of clinical pregnancy at 38 days. The non-inferiority margin was revised to -10% when trial investigators observed a higher-than-expected response rate (approx. 40% compared to the initial estimate of 30%). The TGA Delegate’s Overview expressed concerns over the validity (method) and acceptability (wide margin in the ART context)

over the revised non-inferiority margin. However, the Delegate's Overview acknowledged that there was precedence for the 9%-10% non-inferiority margin within the ART context, including studies comparing the impact of progesterone products, and that the difference between 9% and 10% was minimal in this situation. Subsequently, the PBAC considered the 9-10% margins and post hoc change appeared, on balance, acceptable. The submission also noted that the 10% non-inferiority margin was previously considered by PBAC for Endometrin (Endometrin public summary documentary (PSD) March 2014 PBAC Meeting) and Utrogestan (Utrogestan PSD March 2016 PBAC Meeting).

- 6.8 Overall, most of the trial characteristics and eligibility criteria were consistent with the proposed listing. While the characteristics of the patients in the included trials (of Cyclogest, Utrogestan, Endometrin and Crinone) were similar to the Australian setting, it is noteworthy that the average ages of patients in these trials were approximately 2-3 years younger than Australian women who undergo ART (average age of 35.9), and that 25.4% of Australian women receiving ART in 2018 were over 40, whereas the trial inclusion criterion on age was 18-40 years old (Newman et al 2020).⁵ Therefore, the clinical effectiveness may be lower in practice.
- 6.9 There were two key differences in the treatment details between the included trials and the requested PBS listing. First, treatments were administered for up to 10 weeks (to approximately 12 weeks of gestation). This is consistent with TGA approval and the ACM's comment that while progesterone supplementation was generally continued until a positive β -hCG test result, many clinicians continue until 8-12 weeks' gestation (Cyclogest ACM minutes). The summary of mean dosage in trial ACT-CYC-300-2013-01 showed that approximately 45% of patients continued to receive treatment at 38 days (since oocyte retrieval). In the current PBS listing for other progesterone brands, the maximum quantity per prescription for Utrogestan, Endometrin, and Oriprio is sufficient for approximately 2-6 weeks of treatment, while that for Crinone would be 2 weeks if used twice-daily but might be sufficient for up to 4 weeks if used once daily. The submission's proposed listing of Cyclogest provides 2 weeks of treatment (14-15 days). Second, only one trial, KAD 93, examined Crinone BID (versus Utrogestan TID). There is therefore insufficient evidence to establish the non-inferiority in clinical efficacy and safety of Cyclogest BID to Crinone BID.
- 6.10 In all progesterone trials included in the submission, with the exception of Ng et al (2007) which compared the side effects of Cyclogest to Endometrin, the efficacy outcomes included clinical pregnancy, ongoing pregnancy and biochemical pregnancy rates. The outcome assessment times slightly varied across trials. Only two trials (Michnova et al 2017 and 2004-02) examined live birth rates.

⁵ NEWMAN, J. E., PAUL, R. C. & CHAMBERS, G. M. 2020. Assisted reproductive technology in Australia and New Zealand 2018. Sydney: National Perinatal Epidemiology and Statistics Unit, the University of New South Wales, Sydney.

Comparative effectiveness

6.11 In the trial ACT-CYC-300-2013-01 comparing Cyclogest and Crinone, the primary outcome was the clinical pregnancy rate (defined by the presence of foetal heartbeat by transvaginal ultrasound) at Day 38, and was analysed with both the full analysis set (FAS) and the per protocol (PP) populations. The secondary outcomes included ongoing pregnancy at 70 days, biochemical pregnancy rate at 18 days and 30 days. The FAS population included all patients who received at least one dose of vaginal study medication with transvaginal ultrasound assessments on visit Day 38 concerning foetal heart movement (unless they showed a negative biochemical pregnancy test on Day 18, were diagnosed with miscarriage before Day 38 or a result of biochemical pregnancy test on Day 18 is available). The PP population included all patients who belonged to the FAS who have no major protocol deviations that would interfere with the interpretation of efficacy data. The results of the trial are shown in the table below.

Table 4: Results for key outcomes in trial ACT-CYC-300-2013-01

	Full analysis set			Per protocol analysis		
	Cyclogest	Crinone	Difference (lower limit of 97.5% CI)	Cyclogest	Crinone	Difference (lower limit of 97.5% CI)
Clinical pregnancy at 38 days	141 / 368 (38.3%)	146 / 366 (39.9%)	-1.6% (-8.6%)	136 / 357 (38.1%)	144 / 356 (40.4%)	-2.4% (-9.5%) *
Ongoing pregnancy at 70 days	126 / 365 (34.5%)	137 / 364 (37.6%)	-3.1% (-10.1%)	124 / 355 (34.9%)	136 / 355 (38.3%)	-3.4% (-10.5%)
Biochemical pregnancy rates at 18 days	171 / 369 (46.3%)	175 / 368 (47.6%)	-1.2% (-8.4%)	165 / 357 (46.2%)	169 / 356 (47.5%)	-1.3% (-8.6%)
Biochemical pregnancy rates at 38 days	150 / 368 (40.8%)	157 / 366 (42.9%)	-2.1% (-9.3%)	145 / 357 (40.6%)	155 / 356 (43.5%)	-2.9% (-10.2%)
Clinical implantation rates at 38 days	26.3%	27.8%	-1.5% (N/A)	26.5%	28.4%	-1.9% (N/A)

Source: Tables 2.5-1 to 2.5-5, pp46-49 of the submission}.

CI = confidence interval; FAS = Full Analysis Set; PP = Per Protocol; N/A = not reported

* Table 11.1, p66 of the CSR report noted "non-inferiority not shown", for the initially defined non-inferiority margin of -9%

6.12 In the FAS population, 38.3% of patients in the Cyclogest arm achieved clinical pregnancy at Day 38 compared to 39.9% in the Crinone arm, resulting in a risk difference of -1.6%, equivalent to a lower 97.5% CI of -8.6%. In the PP population, 38.1% patients in the Cyclogest arm achieved clinical pregnancy compared to 40.4% patients in the Crinone arm, resulting in a risk difference of -2.4% which is equivalent to a lower 97.5% CI of -9.5%. The submission concluded that Cyclogest achieved the (revised) non-inferiority margin of -10%. The PP result did not meet the initial non-inferiority margin of -9%.

6.13 It is noteworthy that Cyclogest did not meet the revised non-inferiority margin of -10% for ongoing pregnancy rate at 70 days in either the FAS or PP populations. The ACM did not speak to the merit of the ongoing pregnancy rate specifically as an endpoint, but

noted that live birth rates would be the ideal and were becoming standard endpoints in ART clinical trials (Cyclogest ACM minutes).

- 6.14 The submission presented the results of two indirect comparisons (using the Bucher method⁶) of Cyclogest BID to Utrogestan TID, and Cyclogest BID to Endometrin BID, through the common comparator of Crinone QD. For the indirect comparisons of Cyclogest versus Utrogestan, the FAS population was analysed in ACT-CYC-300-2013-01 (approx. 95.8% of all randomised patients). In the Utrogestan versus Crinone trials, either the ITT populations (all randomised patients) were assessed (Ganesh et al. 2011, Geber et al. 2007 and KAD 93) or the efficacy populations were examined (Michnova et al. 2017, Simunic et al. 2007). For the indirect comparison of Cyclogest versus Endometrin, the FAS population was analysed in ACT-CYC-300-2013-01 while the ITT (all randomised patients) and Efficacy populations were examined in 2004-02. It was unclear why the PP population in ACT-CYC-300-2013-01 was not included in the indirect comparisons.
- 6.15 Based on the indirect comparison results, the submission concluded that Cyclogest was non-inferior in clinical efficacy compared to Utrogestan 200mg TID, and Endometrin 200mg BID/TID. The indirect comparison results presented in the submission are shown in Table 5 and Table 6.

Table 5: Indirect comparison results of Cyclogest versus Utrogestan for efficacy outcomes

Outcomes	RD (95% CI); p value	RR (95% CI); p value	OR (95% CI); p value
Clinical pregnancy rates ^(a)	0.03 (-0.05, 0.11); p=0.48	1.12 (0.88, 1.41); p=0.35	1.21 (0.83, 1.74); p=0.32
Ongoing pregnancy ^(b)	-0.05 (-0.16, 0.06); p=0.36	0.86 (0.63, 1.17); p=0.34	0.79 (0.49, 1.27); p=0.34
Biochemical pregnancy ^(c)	-0.09 (-0.29, 0.11); p=0.37	0.85 (0.61, 1.19); p=0.34	0.66 (0.28, 1.58); p=0.35

Source: Table 2(a).6.9-11, p125-127 of the submission

(a) 1 trial included for Cyclogest, 4 trials included for Utrogestan. Clinical pregnancies were assessed at Day 38 after oocyte retrieval in the FAS population of ACT-CYC-300-2013-01, Week 7 after embryo transfer in the ITT population of Ganesh et al. (2011), between 2 to 4 weeks after oocyte retrieval in the ITT population of Geber et al. (2007) and between 4 to 6 weeks in the Efficacy population of Simunic et al. (2007). Michnova et al. (2017) did not define the timing of clinical pregnancies. 1

(b) 1 trial included for Cyclogest, 2 trials included for Utrogestan. Ongoing pregnancies were assessed at Day 70 after oocyte retrieval in the FAS population of ACT-CYC-300-2013-01. Ongoing pregnancies were assessed at or later than the 12th week of pregnancy in the Efficacy population of Michnova et al. (2017), and 12th week of gestation in the ITT population of KAD 93. Note that in KAD 93, the comparator of Utrogestan was Crinone BID; therefore the indirect comparisons might not be valid.

(c) 1 trial included for Cyclogest, 1 trial included for Utrogestan. Biochemical pregnancies were assessed at Day 18 after oocyte retrieval in the FAS population of ACT-CYC-300-2013-01. The timing was not defined in Michnova et al. (2017).

Abbreviations: CI = Confidence interval; OR = Odds Ratio; RD = Risk Difference; RR = Relative Risk

⁶ BUCHER, H. C., GUYATT, G. H., GRIFFITH, L. E. & WALTER, S. D. 1997. The results of direct and indirect treatment comparisons in meta-analysis of randomised controlled trials. *J Clin Epidemiol*, 50, 683-91.

Table 6: Indirect comparison results of Cyclogest versus Endometrin for efficacy outcomes

Outcome	Comparison	RD (95% CI); p value	RR (95% CI); p value	OR (95% CI); p value
FAS (ACT-CYC-300-2013-01) vs ITT (2004-02)				
Clinical pregnancy	Cyclogest BID vs Endometrin BID	0.02 (-0.08, 0.12); p=0.68	1.04 (0.81, 1.34); p=0.74	1.09 (0.73, 1.64); p=0.67
	Cyclogest BID vs Endometrin TID	-0.02 (-0.12, 0.08); p=0.69	0.96 (0.75, 1.23); p=0.74	0.93 (0.62, 1.40); p=0.73
Biochemical pregnancy ^(a)	Cyclogest BID vs Endometrin BID	0.03 (-0.07, 0.13); p=0.54	1.04 (0.85, 1.28); p=0.69	1.09 (0.73, 1.63); p=0.67
	Cyclogest BID vs Endometrin TID	-0.04 (-0.14, 0.06); p=0.43	0.92 (0.75, 1.12); p=0.38	0.84 (0.56, 1.25); p=0.40
FAS (ACT-CYC-300-2013-01) vs Efficacy (2004-02)				
Clinical pregnancy	Cyclogest BID vs Endometrin BID	0.01 (-0.09, 0.11); p=0.84	1.04 (0.82, 1.34); p=0.74	1.08 (0.72, 1.63); p=0.71
	Cyclogest BID vs Endometrin TID	-0.03 (-0.13, 0.07); p=0.55	0.95 (0.75, 1.21); p=0.68	0.92 (0.61, 1.39); p=0.70
Biochemical pregnancy ^(a)	Cyclogest BID vs Endometrin BID	0.02 (-0.08, 0.12); p=0.69	1.03 (0.84, 1.26); p=0.76	1.09 (0.73, 1.63); p=0.67
	Cyclogest BID vs Endometrin TID	-0.05 (-0.15, 0.05); p=0.32	0.91 (0.74, 1.11); p=0.33	0.82 (0.55, 1.23); p=0.33

Source: Tables 2(b).6.3 and 2(b).6.4, p35-37 in Appendix 1 of the Submission;

(a) Biochemical pregnancy was assessed at Day 18 after oocyte retrieval in ACT-CYC-300-2013-01 and Day 12-14 after embryo transfer in 2004-02.

Abbreviations: BID = Twice daily; CI = Confidence interval; ET = Embryo transfer; FAS = Full Analysis Set; ITT = Intention-to-treat; OR = Odds Ratio; QD = Once daily; RD = Risk Difference; RR = Relative Risk; TID = Three times daily

6.16 The indirect comparisons contained some biases in favour of Cyclogest. First, the PP population in ACT-CYC-300-2013-01 was not included in the indirect comparisons; such omission biases the indirect comparison results in favour of Cyclogest. Second, the submission noted that the ACT-CYC-300-2013-01 population was slightly younger than those in the 2004-02 trial for Endometrin, and the clinical pregnancy rates in both trials were higher for women younger than 35 years of age. This bias is in favour of Cyclogest against Endometrin. Third, patient characteristics and timing of outcome assessment in Utrogestan trials were different from those in the ACT-CYC-300-2013-01 (as noted in the submission); while these biases might be in favour or against Cyclogest, they create uncertainty in the conclusion of non-inferiority. Fourth, the indirect comparison of Cyclogest versus Utrogestan for ongoing pregnancy included the results of KAD 93 trial which compared Utrogestan TID with Crinone BID. Pooling Crinone QD and BID in one comparative analysis is not appropriate, and increased the uncertainty in the conclusion of non-inferiority.

Comparative harms

6.17 The safety population in ACT-CYC-300-2013-01 consisted of patients who received at least one dose of study medication (99.9% of all randomised patients). The adverse events as reported in the trial are shown below.

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Table 7: Summary of key adverse events in ACT-CYC-300-2013-01

	Cyclogest N=385	Crinone N=383	Risk Difference (95% CI); p value
Any AE	168 (43.6)	171 (44.6)	-0.01 (-0.08, 0.06); p=0.78
Any serious AE	6 (1.6)	13 (3.4)	-0.02 (-0.04, 0.00); p=0.10
Drug-related AEs	58 (15.1)	55 (14.4)	0.01 (-0.04, 0.06); p=0.78
Drug-related SAEs†	0	0	0 (-0.01, 0.01); p=1.00
Discontinued due to AE	19 (4.9)	12 (3.1)	0.02 (-0.01, 0.05); p=0.20
Intensity			
Mild AEs	126 (32.7)	133 (34.7)	-0.02 (-0.09, 0.05); p=0.56
Moderate AEs	40 (10.4)	36 (9.4)	0.01 (-0.03, 0.05); p=0.65
Serious AEs	2 (0.5)	2 (0.5)	0 (-0.01, 0.01); 1.00
<u>Related to study drug</u>	58 (15.1)	55 (14.4)	0.01 (-0.04, 0.06); p=0.78
Mild AEs	40 (10.4)	42 (11.0)	-0.01 (-0.05, 0.04); p=0.80
Moderate AEs	17 (4.4)	13 (3.4)	0.01 (-0.02, 0.04); p=0.46
Serious AEs†	1 (0.3)	0	0 (0, 0.01); p=0.48
Deaths†	0	0	0 (-0.01, 0.01); p=1.00

Source: Table 2.5.9, p54 of the submission, Saunders et al. (2020) Table III p 361; ACT-CYC-300-2013-01 CSR Table 14.3.2-3 p 912, Table 14.3.3-1 p 981-982

†0.5 added to test and control cells

Abbreviations: AE = Adverse events; CI = Confidence interval; NE = Not evaluable; SAE = Serious adverse events

The indirect comparisons of Cyclogest versus Utrogestan, and versus Endometrin was presented in

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6.18 Table 8 and Table 9.

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Table 8: Summary of results for the indirect comparison of Cyclogest BID versus Utrogestan TID safety outcomes through to 10-12 weeks

Outcomes	RD (95% CI); p value	RR (95% CI); p value	OR (95% CI); p value
Any AE (a)	-0.01 (-0.10, 0.08); p=0.83	1.01 (0.56, 1.83); p=0.97	0.99 (0.49, 1.99); p=0.98
SAE (b)	-0.02 (-0.05, 0.01); p=0.12	0.16 (0.01, 4.41); p=0.28	0.15 (0.01, 4.36); p=0.27
DISCAE (c)	0.03 (-0.01, 0.07); p=0.10	2.55 (0.67, 9.69); p=0.17	2.62 (0.66, 10.39); p=0.17
Specific adverse events			
Vomiting *	0 (-0.03, 0.03); p=1.00	0.94 (0.06, 13.82); p=0.96	0.94 (0.06, 14.16); p=0.96
Constipation	0 (-0.04, 0.04); p=1.00	NE	NE
Abdominal pain	-0.01 (-0.06, 0.04); p=0.70	0.94 (0.13, 6.78); p=0.95	0.93 (0.12, 7.12); p=0.94
Dizziness	0 (-0.03, 0.03); p=1.00	0.45 (0.02, 11.79); p=0.63	0.45 (0.02, 12.02); p=0.63
Headache	-0.01 (-0.05, 0.03); p=0.65	0.50 (0.04, 5.90); p=0.58	0.50 (0.04, 5.97); p=0.58
Vagina itching #	-0.14 (-0.23, -0.05); p=0.0013	1.08 (0.04, 28.68); p= 0.96	0.92 (0.03, 25.04); p=0.96

Source: Table 2(a)6.13, p129, Table 2(a)6.14, p131, and 2(a)6.15, p132,

Notes: Safety analyses were conducted in patients who received at least one dose of study medication in ACT-CYC-300-2013-01, and patients who completed the safety questionnaires in Simunic et al. (2007) and KAD 93. The population was assumed to be the ITT population in KAD 93.

Treatment duration in ACT-CYC-300-2013-01 and KAD 93 was 10 weeks. Treatment duration in Simunic et al. (2007) was possibly 12 weeks.

* Defined as nausea and/or vomiting in the Simunic et al. (2007) trial.

Defined as application site pruritus in ACT-CYC-300-2013-01.

(a) 1 trial for Cyclogest (ACT-CYC-300-2013-01) and 1 trial for Utrogestan (Simunic et al 2007)

(b) 1 trial for Cyclogest (ACT-CYC-300-2013-01) and 1 trial for Utrogestan (KAD 93); Note that in KAD 93, the comparator of Utrogestan was Crinone BID; therefore the indirect comparisons might not be valid.

(c) 1 trial for Cyclogest (ACT-CYC-300-2013-01) and 2 trials for Utrogestan (Simunic et al 2007, KAD 93). DISCAE are discontinuation rates due to an adverse event or local intolerance for up to 10-12 weeks; Note that in KAD 93, the comparator of Utrogestan was Crinone BID; therefore the indirect comparisons might not be valid.

Abbreviations: BID = Twice daily; CI = Confidence interval; DISCAE = discontinuation rates due to AE; ET = Embryo transfer; FAS = Full Analysis Set; ITT = Intention-to-treat; OR = Odds Ratio; NE = not evaluated; QD = Once daily; RD = Risk Difference; RR = Relative Risk; TEAE = treatment-emergent adverse events; TID = Three times daily

Table 9: Results for the indirect comparison of Cyclogest BID versus Endometrin BID/TID for safety outcomes for up to 10 weeks

Outcome	Comparison	RD (95% CI); p value	RR (95% CI); p value	OR (95% CI); p value
Any AE	Cyclogest BID vs Endometrin BID	-0.02 (-0.12, 0.08); p=0.69	0.96 (0.78, 1.18); p=0.70	0.91 (0.61, 1.36); p=0.66
	Cyclogest BID vs Endometrin TID	-0.03 (-0.13, 0.07); p=0.54	0.95 (0.77, 1.17); p=0.64	0.90 (0.60, 1.34); p=0.59
SAE	Cyclogest BID vs Endometrin BID	-0.03 (-0.06, 0.00); p=0.07	0.30 (0.08, 1.04); p=0.06	0.29 (0.08, 1.05); p=0.06
	Cyclogest BID vs Endometrin TID	-0.02 (-0.05, 0.01); p=0.17	0.52 (0.14, 1.96); p=0.33	0.51 (0.13, 2.01); p=0.34
DISCAE	Cyclogest BID vs Endometrin BID	0.02 (-0.01, 0.05); p=0.22	1.58 (0.09, 28.08); p=0.76	1.60 (0.09, 28.74); p=0.75
	Cyclogest BID vs Endometrin TID	0.01 (-0.02, 0.04); p=0.56	0.23 (0.02, 2.06); p=0.19	0.23 (0.02, 2.09); p=0.19

Source: Table 2(b).6.5, p38-39 in Appendix 1 of the submission

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(a) Safety outcomes for ACT-CYC-300-2013-01 were derived from patients who experienced TEAEs, whereas 2004-02 trial did not report whether AEs were TEAEs or non-TEAEs.

Abbreviations: BID = Twice daily; CI = Confidence interval; ET = Embryo transfer; FAS = Full Analysis Set; ITT = Intention-to-treat; OR = Odds Ratio; QD = Once daily; RD = Risk Difference; RR = Relative Risk; TEAE = treatment-emergent adverse events; TID = Three times daily

6.19 Similar to the indirect comparison of efficacy outcomes, the indirect comparison of safety outcomes were uncertain due to differences in the populations, treatment duration and the definitions of adverse events. However, it was noted in the TGA Delegate's Overview that progesterone products have similar safety profiles.

Benefits/harms

6.20 As the claim was for non-inferiority, information on the benefits and harms was not presented in the evaluation.

Clinical claim

6.21 The submission described Cyclogest 400 mg progesterone vaginal pessaries BID as non-inferior in terms of efficacy and safety compared with Crinone 8% (90 mg) progesterone vaginal gel QD.

6.22 The evaluation and ESC noted the safety claim was adequately supported. However, the following issues were identified regarding the efficacy claim: (1) the revised non-inferiority margin from -9% to -10% at the lower 95% confidence interval, and (2) the applicability of the clinical outcomes examined at 38 days (and up to 70 days) of treatment to the shorter treatment duration of 14-15 days. Additionally, there are no trials or studies available to assess the comparative efficacy of Cyclogest BID versus Crinone BID. The Pre-Sub-Committee Response (PSCR) and pre-PBAC response noted that Crinone QD or BID are alternate recommended regimens in the TGA-approved Product Information (PI) and that although most women will respond to the once daily regime, some women may need 90 mg twice daily. The PSCR and pre-PBAC response also noted the PBAC has previously considered that there was no clinical evidence of '...the superiority of higher progesterone doses over lower doses' (Utrogestan PSD July 2016 para 7.2) and has previously accepted the once daily or twice daily regimens where Crinone is a comparator (Endometrin PSD March 2014, Utrogestan PSD March 2016).

6.23 The submission also described Cyclogest 400 mg BID as non-inferior in terms of efficacy and safety compared to Utrogestan TID, and Endometrin BID/TID. The PBAC considered the clinical claim against Utrogestan and Endometrin to be uncertain, but accepted the supplemental evidence to the main evidence of comparative efficacy and safety of Cyclogest and Crinone.

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

Economic analysis

6.25 The submission presented a cost-minimisation analysis. The key assumptions and components of the cost-minimisation approach are summarised in the table below.

Table 10: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on the evidence presented in Section 2, effectiveness of Cyclogest 400 mg BID is assumed to be non-inferior to <ul style="list-style-type: none"> • Crinone 8% (90 mg) QD • Utrogestan 200 mg TID in terms when used for luteal phase support as part of an ART treatment cycle.
Therapeutic claim: safety	Based on the evidence presented in Section 2, safety of Cyclogest 400 mg BID is assumed to be non-inferior to <ul style="list-style-type: none"> • Crinone 8% (90 mg) QD • Utrogestan 200 mg TID
Evidence base	<ul style="list-style-type: none"> • Direct comparison of Cyclogest 400 mg BID and Crinone 8% (90 mg) QD from a randomised, open-label trial (ACT-CYC-300-2013-01) • An indirect comparison of Cyclogest 400 mg BID and Utrogestan 200 mg TID as a supplementary comparator
Equi-effective doses	<ul style="list-style-type: none"> • Cyclogest 400 mg BID \equiv Crinone 8% (90 mg) QD • Cyclogest 400 mg BID \equiv Utrogestan 200 mg TID
Direct medicine costs	Direct cost of treatment for Cyclogest and the comparator
Other costs or cost offsets	All medications are self-administered at home and cover the same treatment period of 14-15 days; No other costs or cost offsets resulting from differences in prescribing, administration, medicine-specific monitoring, or management of adverse events were considered because the two medicines have the same active ingredient of progesterone.

Source: Table 3.1-1, p146 and Table 3(a).1.1 p152 of the submission.

Abbreviations: BID = Twice daily; QD = Once daily; TID = Three times daily

- 6.26 The equi-effective doses were estimated as: 2 packs Cyclogest 400 mg progesterone vaginal pessaries, 15 applications per pack, BID \equiv 1 pack of Crinone 8% (90 mg), 15 applications per pack, QD, over the 14-15 days of treatment. The dosage was consistent with the key clinical trial ACT-CYC-300-2013-01 and the PI. The submission, however, did not cost-minimise Cyclogest against Crinone, based on the argument that Crinone was not the lowest cost drug out of all progesterone brands on the PBS.
- 6.27 The submission identified Utrogestan 200 mg TID as a relevant alternative therapy. This was reasonable. The equi-effective doses were estimated as: 2 packs Cyclogest 400 mg progesterone vaginal pessaries, 15 applications per pack, BID \equiv 1 pack Utrogestan 200 mg, 42 applications per pack, TID, over the 14-15 days of treatment. The dosage was consistent with the clinical trials presented in the submission. The submission then cost minimised Cyclogest to Utrogestan, based on the argument that Utrogestan is the lowest cost drug of all progesterone brands on the PBS.
- 6.28 No additional cost or cost offsets were included in the analysis. This approach was consistent with the cost-minimisation analysis of Utrogestan versus Crinone (PSD March 2016 PBAC Meeting), and Endometrin versus Crinone (PSD March 2014 PBAC Meeting).
- 6.29 The submission proposed an AEMP of \$37.77 per pack, which equates to an AEMP of \$75.53 for the maximum quantity (i.e. \$37.77 x 2, accounting for rounding).
- 6.30 The results of the analysis, based on published prices, are shown in the table below. Overall, the price of Cyclogest should be no higher than the lowest cost comparator for progesterone currently listed on the PBS.

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Table 11: Results of the cost-minimisation analysis

	Cyclogest 400 mg BID	Utrogestan 200 mg TID
Prescriptions		
Prescriptions per treatment course	1	1
Units per treatment course		
Duration of treatment course (days)	15	14
Units per day	2	3
Units per treatment course	30 [15 x 2]	42 [14 x 3]
Quantity per prescription		
Units per pack	15	42
Packs per script	2 packs [30/15]	1 pack [42/42]
Cost per treatment course		
AEMP per pack	\$37.77	\$75.53
AEMP per treatment course	\$75.53 [\$37.77 x 2 packs]	\$75.53 [\$75.53 x 1 pack]

Source: Table 3(a).3-2 p155 of the submission

Abbreviations: AEMP = approved ex-manufacturer price. BID = Twice daily; Max = maximum; QD = Once daily; qty = quantity; TID = Three times daily

Estimated PBS usage & financial implications

6.31 This submission was not considered by DUSC. The submission used a market share approach, assuming that Cyclogest will substitute for other progesterone brands that are currently listed on the PBS, including Crinone, Utrogestan, Endometrin, and Oripo. The evaluator considered this to be reasonable.

6.32 The key inputs for the financial estimates are shown in the table below.

Table 12: Key inputs for financial estimates

Data	Value	Source	Comment
Predicted prescriptions			
Predicted prescriptions for all progesterone medicines on the PBS for luteal phase support	Yr 1: 1 Yr 2: 1 Yr 3: 1 Yr 4: 2 Yr 5: 2 Yr 6: 2	Services Australia PBS statistics for item numbers 6366C (Crinone), 10116K (Endometrin), 10930G (Utrogestan), 9608Q (Oripo 100), and 9609R (Oripo 200).	A number of steps were used; The linear growth assumption may be reasonable.
Treatment utilisation			
Uptake rate	Yr 1: % Yr 2: % Yr 3: % Yr 4: % Yr 5: % Yr 6: %	Assumption by the Sponsor	No justification for the uptake rates. Patient preference data favoured the comparator Crinone (p.51 in the submission)
Quantity (packs) dispensed per prescription	<u>Packs/script</u> Crinone = 1.93 Endometrin = 1.95 Utrogestan = 1.00 Oripo 100 = 2.80 Oripo 200 = 2.44	Estimated based on benefits paid and services processed by Services Australia in the 2021 calendar year.	Verified
Scripts (quantity / packs) dispensed	Yr 1: 3 Yr 2: 4 Yr 3: 5 Yr 4: 5	Based on the assumed uptake rates and a script equivalence of 1:1 for Cyclogest to each individual	High uncertainty due to: <ul style="list-style-type: none"> • Uptake rate (assumed) • Estimated market shares for individual progesterone

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Data	Value	Source	Comment
	Yr 5: [redacted] ⁶ Yr 6: [redacted] ⁶	brand of progesterone on the PBS	medications and number of scripts There is a risk that the magnitude of the net impact on the PBS might be overestimated
Costs			
Cyclogest 400 mg x 15 pessaries	AEMP: \$37.77	Requested price	
Alternative progesterone brands: • Crinone • Utrogestan • Endometrin • Oriprio 100 • Oriprio 200	<ul style="list-style-type: none"> • Crinone 8% vaginal gel, 90 mg = \$120.62 (per pack) • Endometrin 100 mg x 21 pessaries = \$40.12 • Utrogestan 200 mg x 42 capsules = \$75.53 • Oriprio 100 mg x 15 pessaries = \$47.88 • Oriprio 200 mg x 15 pessaries = \$52.82 	Schedule of Pharmaceutical Benefits <ul style="list-style-type: none"> • 6366C (Crinone), • 10116K (Endometrin) • 10930G (Utrogestan) • 9608Q (Oriprio 100) • 9609R (Oriprio 200) 	Some current PBS-listed progesterone medications might have SPAs that result in lower costs to the government than the proposed listing price for Cyclogest. The net impact on PBS budget might be overestimated. The submission cited the incorrect price for Oriprio 200 mg; The evaluation noted it should be \$35.40. The ESC noted the impact of the price difference is likely to be very small due to the relatively small market share of Oriprio in this setting.
Patient copayment	General ordinary: \$42.50 General safety net: \$6.80 Concessional ordinary: \$6.80 RPBS ordinary: \$6.80	PBS website	Verified

Source: Source: Table 4.1.4, pp157-158 of submission, and the financial estimate spreadsheet of submission, 'Cyclogest (progesterone) - UCM.xlsx'.

The redacted values correspond to the following ranges:

¹ 50,000 to < 60,000

² 60,000 to < 70,000

³ 500 to < 5,000

⁴ 5,000 to < 10,000

⁵ 10,000 to < 20,000

⁶ 20,000 to < 30,000

6.33 The submission assumed a linear market growth of the number of prescriptions for all progesterone medicines on the PBS for luteal phase support based on the past progesterone market data dated July 2016-December 2020. The linear growth assumption may be reasonable.

6.34 The average quantity (number of packs) dispensed per prescription for Crinone was 1.93, indicating that in practice, patients might use Crinone QD for a longer treatment period (15 applications x 2 packs ~ up to 4 weeks QD), or patients might use Crinone BID, against which Cyclogest has no comparative evidence of clinical efficacy and safety, or there would be wastage beyond the treatment duration of 14-15 days.

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- 6.35 To estimate the substitution of other progesterone brands by Cyclogest, the submission undertook a number of steps that either introduced unnecessary distortion to the data or calculation inconsistencies. The submission calculated two sets of prescription numbers for the whole progesterone market, between which the difference increased from 5,000 to < 10,000 (year 2022) to 10,000 to < 20,000 (year 2027), corresponding to 13-20% of the total script estimates in a given year. The set with larger number of prescriptions was then used for the financial estimates, which favours Cyclogest.
- 6.36 The evaluator estimated the total scripts for all progesterone products using the annual data (2017-2021, using an exponential function, R2 = 92%) and noted that these estimates fall between these two sets of estimations in the submission (see **Error! Reference source not found.**, Row D). The market share estimates used to predict the number of scripts for Cyclogest were therefore highly uncertain. The PSCR and pre-PBAC response maintained that irrespective of the approach taken to calculate the financial estimates, a listing for Cyclogest would be associated with a net cost saving to the Government.
- 6.37 The estimated number of prescriptions for all progesterone brands currently listed on the PBS and predicted Cyclogest scripts, and the estimated financial implications of listing Cyclogest on the PBS are shown in the table below.

Table 13: Estimation of use and financial implications

		2021 (a)	2022	2023	2024	2025	2026	2027
A	Predicted number of prescriptions							
A1	Crinone	23,014	1	1	1	1	1	1
A2	Endometrin	1,589	2	2	2	2	2	2
A3	Utrogestan	18,006	3	3	3	3	1	1
A4	Oripro100	48	4	4	4	4	4	4
A5	Oripro200	6,270	5	5	5	5	5	5
	Total	48,927	6	6	7	7	7	7
B	Estimated market share for each progesterone medication							
B1	Crinone		%	%	%	%	%	%
B2	Endometrin		%	%	%	%	%	%
B3	Utrogestan		%	%	%	%	%	%
B4	Oripro100		%	%	%	%	%	%
B5	Oripro200		%	%	%	%	%	%
C	Estimated number of scripts for each progesterone medication							
C1	Crinone		1	1	1	1	1	1
C2	Endometrin		2	2	2	2	2	2
C3	Utrogestan		1	1	1	1	1	10
C4	Oripro100		4	4	4	4	4	4
C5	Oripro200		5	5	5	5	5	5
	Total		7	7	7	9	9	9
D*	Estimated total number of scripts for all progesterone brands (linear growth, annual scripts, 2015-2021)		6	7	7	7	9	9
E	Uptake rate – Cyclogest	Assumed	%	%	%	%	%	%
F	Substituted prescriptions							
F1	Crinone	Scripts 2022	-2	-2	-5	-5	-5	-3

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		2021 (a)	2022	2023	2024	2025	2026	2027
F2	Endometrin	= scripts	-4	-4	-4	-4	-4	-4
F3	Utrogestan	2021 *	-2	-2	-2	-5	-5	-3
F4	Oripro100	(1+B)	-4	-4	-4	-4	-4	-4
F5	Oripro200	B rows in Table 4.2.1	-4	-2	-2	-2	-2	-2
F	Total number of substituted scripts	Sum of F1 to F5	-2	-5	-3	-3	-1	-1
G	Prescriptions dispensed for Cyclogest	Equals - F	2	5	3	3	1	1
Net financial implications of listing Cyclogest on the PBS								
	Patients copayments		\$ ⁸	\$ ⁸	\$ ⁸	\$ ⁸	\$ ⁸	\$ ⁸
	PBS/RPBS cost reduction of other brands (excluding co-payments)		-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸
	PBS/RPBS cost of Cyclogest		\$ ⁸	\$ ⁸	\$ ⁸	\$ ⁸	\$ ⁸	\$ ⁸
	PBS/RPBS cost net patient co-payment		-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸

Source: Tables 4.2.1, 4.2.2 and 4.2.3 in pp159-160 of the submission, Tables 4.3-2, p163 and 4.4.1, p165 of the submission, and Sheets 2a.Scripts – Market and 12a.Scripts - trend, excel file Cyclogest (progesterone) – UCM, Table 4.2.1, p159 in the submission, and calculated during the evaluation

*Calculated during the evaluation

(a) Actual number of prescriptions in 2021

The redacted values correspond to the following ranges:

¹ 20,000 to < 30,000

² 500 to < 5,000

³ 10,000 to < 20,000

⁴ < 500

⁵ 5,000 to < 10,000

⁶ 40,000 to < 50,000

⁷ 50,000 to < 60,000

⁸ \$0 to < \$10 million

⁹ 60,000 to < 70,000

¹⁰ 30,000 to < 40,000

6.38 The net cost savings to the PBS/RPBS of listing Cyclogest was estimated to rise steadily to approximately \$0 to < \$10 million in Year 6 (2027), and a total of \$0 to < \$10 million in the first 6 years of listing (2022-2027). The PBAC noted these costs were based on the published price of the comparator. The projected net cost savings to the PBS will be lower once the effective price of the comparator is applied.

6.39 In the sensitivity analysis, the submission presented alternative methods to calculate the predicted used of Cyclogest, including different moving average choice and alternative trendlines for the market share prediction of each progesterone brand. The submission concluded that the net financial implications for the health budget were most sensitive to the trendline used to extrapolate the total number of progesterone prescriptions. The submission did not examine the key assumption of Cyclogest’s uptake rate, for which a sensitivity analysis was added by the evaluator. The sensitivity analyses are presented in the table below.

Table 14: Results of sensitivity analysis

Net impact for the health budget	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 1-6
	2022	2023	2024	2025	2026	2027	2022-27

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Base case	-\$1 ¹	-\$1 ¹	-\$1 ¹	-\$1 ¹	-\$1 ¹	-\$1 ¹	-\$1 ¹
Total scripts estimation: moving average of 1 month	0.15%	0.29%	0.42%	0.53%	0.64%	0.73%	0.56%
Total scripts estimation: moving average of 12 month	0.06%	0.11%	0.16%	0.21%	0.25%	0.28%	0.22%
Market share of scripts: logarithmic extrapolations	-3.83%	-7.51%	-11.01%	-14.30%	-17.38%	-20.27%	-15.31%
Slow uptake rate (█%, █%, █%, █%) (a)	0.00%	-23.08%	-25.00%	-23.08%	-19.35%	-14.29%	-19.15%
Different set of scripts estimates (set 1) (a)(b)	-4.82%	-4.82%	-4.82%	-4.82%	-4.83%	-4.83%	-4.83%

Source: Table 4.6-1, p 167 of the submission and calculated during the evaluation

(a) Sensitivity analysis calculated during the evaluation

(b) The submission estimated the number of scripts for each progesterone brand for the period 2021-2027 (referred to as set 1 here), then calculated their respective market growth rates, and then applied these rates to the number of scripts observed (actual) in 2021 to predict the number of scripts for each brand for period 2022-2027 (referred to as set 2 here). Set 2 estimates was used in the financial impact analysis in the submission; the submission noted that the method (to derive set 1) seemed to underestimate the number of scripts in 2021.

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

Quality Use of Medicines

6.40 All progesterone brands on the PBS are currently listed for the treatment duration of 14-15 days per prescription (treatment course). In practice, patients who are on Crinone can extend the treatment time to approximately 4 weeks if using one application per day [15 applications x 2 packs maximum quantity ~ 4 weeks of treatment QD]. Similarly, Endometrin can be used TID or BID with a maximum quantity of 42 for a longer period than 2 weeks of treatment [21 application x 2 packs ~ 3 weeks BID]. If Oripro is used at the dosage of 200 mg daily the maximum quantities provide treatment for over 6 weeks for Oripro 200 mg and just over 3 weeks for Oripro 100 mg. Therefore, there might be wastage and/or extended treatment duration, depending on the treating clinicians. The PBAC noted the quantity as per the proposed listing of Cyclogest will be sufficient for luteal phase support consistent with Crinone, Utrogestan and Endometrin when used at the maximum recommended dose.

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 progesterone 400 mg pessary (Cyclogest®) on the basis it should be available only under special arrangements covered under the PBS Section 100 – IVF Program for the treatment of infertile women who require luteal phase support as part of an Assisted Reproductive Technology (ART) treatment cycle. The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of Cyclogest would be acceptable if it were cost-minimised against the least costly progesterone for luteal phase support currently listed on the PBS.

- 7.2 The PBAC accepted the nominated main comparator Crinone® 8% (90 mg) progesterone vaginal gel. The PBAC also accepted Utrogestan 200 mg micronised progesterone vaginal capsules TID and Endometrin 100 mg micronised progesterone vaginal pessaries BID/TID as alternative therapies on the basis that they are alternative progesterone brands on the PBS for the same target population. The PBAC accepted the equi-effective doses to be: Cyclogest 400 mg BID \equiv Crinone® 8% (90 mg) QD and Cyclogest 400 mg BID \equiv Utrogestan® 200 mg TID.
- 7.3 The PBAC considered that the claim of non-inferior comparative effectiveness to Crinone was reasonable and was supported by the key trial ACT-CYC-300-2013-01, which compared Cyclogest 400 mg vaginal pessaries BID to Crinone 8% (90 mg) vaginal gel QD. The submission concluded that Cyclogest achieved the (revised) non-inferiority margin of -10% where the Cyclogest arm achieved clinical pregnancy at Day 38 compared to in the Crinone arm. Although the results for the proportion of clinical pregnancy at 38 days had a revised non-inferiority margin from -9% to -10% at the lower 95% confidence interval, the PBAC considered this to be acceptable given a non-inferiority limit of -10% had previously been accepted when the PBAC considered Endometrin and Utrogestan (Endometrin PSD March 2014, Utrogestan PSD March 2016).
- 7.4 The PBAC noted the difference in treatment length between the clinical trials presented in the submission where the clinical outcomes were examined at 38 days (and up to 70 days) of treatment compared to the shorter treatment duration of 14-15 days of treatment in clinical practice. The PBAC considered a treatment duration of 2 weeks with Cyclogest for luteal phase support would be appropriate for the PBS listing as it would be consistent with Crinone, Utrogestan and Endometrin when used at the maximum recommended dose.
- 7.5 The PBAC accepted the non-inferior safety claim which was supported by the clinical data which demonstrated no significant difference in adverse effects between Cyclogest and Crinone. The PBAC noted that progesterone products have similar safety profiles and adverse events would be manageable in clinical practice.
- 7.6 The PBAC noted that the submission presented a cost-minimisation analysis between Cyclogest and Utrogestan, based on the argument that Utrogestan is the lowest cost drug of all progesterone brands on the PBS. The PBAC accepted that the price of Cyclogest should be no higher than the lowest cost comparator for progesterone for luteal phase support currently listed on the PBS.
- 7.7 The PBAC agreed with the submission assumption that Cyclogest will substitute for other progesterone brands that are currently listed on the PBS, including Crinone, Utrogestan, Endometrin, and Oriprio. The PBAC considered that listing Cyclogest may result in a net cost saving to Government if it replaces other progesterone brands that are listed at a higher price.
- 7.8 The PBAC considered the requested maximum quantity of 30 units and nil repeats to be

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appropriate and aligned with the TGA approved product information for Cyclogest. The PBAC considered the requested treatment duration of approximately 2 weeks for Cyclogest for luteal phase support was reasonable and was consistent with other PBS listings for progesterone for the same indication.

- 7.9 The PBAC also noted that consistent with the Section 100 – IVF listed medicines policy, repeats are not permissible for these medicines, however prescribers may request prior approval to prescribe an additional quantity if a patient requires a quantity beyond the PBS listed maximum quantity. Therefore, the PBAC advised the following administrative advice regarding maximum repeats be added to the Cyclogest restriction and this should flow-on to all medicines listed under the Section 100 IVF program: “No increase in the maximum number of repeats may be authorised”.
- 7.10 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Cyclogest is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over other PBS listings for progesterone for luteal phase support, 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 2022* for Pricing Pathway A were not met.
- 7.11 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
PROGESTERONE					
progesterone 400 mg pessary, 15	NEW	2	30	0	Cyclogest
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: Section 100 – IVF Program					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [4997]					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Indication: Assisted Reproductive Technology					
Clinical criteria:					

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	The treatment must be for luteal phase support as part of an assisted reproductive technology (ART) treatment cycle for infertile women
	AND
	Clinical criteria:
	Patients must be receiving medical services as described in items 13200 or 13201 of the Medicare Benefits Schedule
	Prescribing Instructions: The luteal phase is defined as the time span from embryo transfer until implantation confirmed by positive B-hCG measurement

8.2 The Administrative Advice 'No increase in the maximum number of repeats may be authorised' is to be flowed on to all PBS-listed items under the PBS Section 100 – IVF Program. The list of items can be found at: <https://www.pbs.gov.au/browse/section100-if>

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 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.

10 Sponsor's Comment

The sponsor had no comment.