

6.09 PROGESTERONE, Capsule 200 mg, Utrogestan® Besins Healthcare Australia Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested a General Schedule, Authority Required (STREAMLINED) listing for progesterone (Utrogestan®) for the prevention of preterm birth in women with singleton pregnancies and a short cervix (≤ 25 mm) and/or a history of preterm birth.
- 1.2 Listing was requested on the basis of a clinical claim of superior efficacy and non-inferior safety supported by a cost analysis.

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

Component	Description
Population	Pregnant women (singleton pregnancy) with a short cervix and/or a history of spontaneous preterm birth.
Intervention	Progesterone (Utrogestan) soft capsule 200 mg (for vaginal use) once daily, recommended at bedtime.
Comparator	Standard of Care (SOC)
Outcomes	Reduction in risk of preterm birth; time to preterm birth/pregnancy prolongation; frequency of spontaneous preterm birth; respiratory distress syndrome; neonatal morbidity and mortality; low birth weight; admission to neonatal intensive care unit.
Clinical claim	Treatment with Utrogestan in women with a short cervix and/or history of spontaneous preterm birth is well tolerated and more effective than SOC in the prevention of preterm birth.

Source: Table 1.1, p21 of the submission.

2 Background

Registration status

- 2.1 Utrogestan received TGA approval for use in women at risk of preterm birth in singleton pregnancies on 12 November 2019. The TGA approved indication is: "Prevention of preterm birth in women with singleton pregnancy who have a short cervix (mid-trimester sonographic cervix ≤ 25 mm) and/or a history of spontaneous preterm birth".

3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Public Summary Document – November 2020 PBAC Meeting

MEDICINAL PRODUCT, medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
PROGESTERONE progesterone 200 mg capsule, 42	NEW	1	42	3	Utrogestan

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
Condition: Pregnancy Prevention of preterm birth
Indication: Support during pregnancy Prevention of preterm birth
Treatment Phase: Initial treatment [blank]
Clinical criteria:
Patient must be pregnant
AND
Clinical criteria:
Patient must have a singleton pregnancy
AND
Clinical criteria:
Patient must have a short cervix (midtrimester sonographic cervix ≤ 25 mm); <i>and/or</i>
Patient must have a history of spontaneous preterm birth
AND
Population criteria:
Female
Administrative Advice:
No increase in the maximum quantity or number of units may be authorised.
Administrative Advice:
No increase in the maximum number of repeats may be authorised.

3.2 The proposed maximum quantity of 1 pack of 42 capsules and 3 repeats would allow for the maximum recommended duration of treatment, which is 20 weeks. Treatment is initiated during the second trimester (16-24 weeks gestation) and is to be continued to the end of gestation. The requested amount, including the 3 repeats, would actually provide for 24 weeks of treatment. The product information (PI) stated that the usual dose is 200 mg/day, and that treatment is to be continued until the end of the 36th week of gestation or until delivery. Thus, it is possible that treatment could commence at week 16 and continue until week 40.

3.3 The PBAC considered progesterone should be initiated after the first trimester of pregnancy (not prior to 16 weeks gestation), and that this should be specified in the restriction.

3.4 The requested restriction was consistent with the approved TGA indication.

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

4 Population and disease

- 4.1 The submission stated (p15) that preterm birth was the single greatest cause of death and disability in children up to 5 years of age in the developed world. The submission indicated that based on 2018 Australian Institute of Health and Welfare (AIHW) data: spontaneous preterm birth accounted for around 14% of perinatal deaths in Australia; and infants born prior to 32 weeks gestation were at increased risk of complications in infancy and contributed to more than 50% of all perinatal mortality. The submission added that preterm birth was associated with long-term neurological disability, admission to neonatal intensive care, severe morbidity in the first weeks of life, prolonged hospital stay after birth, readmission to hospital in the first year of life and increased risk of chronic lung disease. These latter claims were sourced from the World Health Organization (WHO) as part of a global report on preterm birth (2012). The ESC acknowledged the risk factors of previous spontaneous pre-term birth and a short cervix on ultrasound, in line with the restriction criteria, and also identified additional risk factors of smoking, Aboriginal and Torres Strait Islander descent and lack of support/socio-economic disadvantage.
- 4.2 The submission cited Royal Australia and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) clinical guidelines and stated that all Australian and most international guidelines recommend the use of progesterone for prevention of preterm birth. The submission stated (p16) that Australian Department of Health recommendations included progesterone under its Pregnancy Guidelines, and lack of PBS access for all women was at odds with this recommendation and resulted in inequity of access to treatment. The PBAC noted that a large number of clinical guidelines supported the use of progesterone for prevention of preterm birth in the proposed PBS population, including the NICE guidelines on preterm labour and birth¹.
- 4.3 The submission also noted that prevention of preterm birth in Aboriginal and Torres Strait Islander (Indigenous) families is a major public health priority in Australia and noted that based on 2014 AIHW data, approximately 14% of babies of indigenous mothers were born preterm, compared to 8% of babies of non-indigenous mothers. The submission cited Newnham (2020), which indicated that a suite of interventions including progesterone resulted in a significant reduction in preterm birth rates in women in the Kimberley region classified as low risk. While the Newnham (2020) paper indicated that high and low risk was based on maternal characteristics including age, ethnicity, smoking, socioeconomic status, medical conditions and obstetric history, no information was provided as to the definition of low risk that was used. The Newnham (2020) paper also indicated there was no advantage

¹ NICE guideline NG25 2015: Preterm labour and birth. Available at: <https://www.nice.org.uk/guidance/ng25/resources/preterm-labour-and-birth-pdf-1837333576645>

observed for women at high risk. Thus, the applicability of the benefit cited by the submission to the proposed PBS population was not clear.

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

5 Comparator

- 5.1 The submission nominated standard of care (SOC) as the main comparator. The main reason for the nomination of SOC as the comparator was that there was no other treatment on the PBS for the proposed indication, and SOC was in line with Australian guidelines and Australian clinical practice.
- 5.2 The submission included cervical cerclage as an example of SOC, but did not further justify the inclusion of this surgical procedure. Current guidelines appear to suggest that cervical cerclage can be used where there is both a history of preterm birth and a short cervix, and the ESC considered that it is especially useful with progressive cervical shortening; therefore, cervical cerclage would be appropriate for a proportion of the proposed PBS population. The ESC noted that Western Australian clinical guidelines indicate that cervical cerclage may be used as part of a stepped approach with or without progesterone.
- 5.3 The submission identified Oriprio® (progesterone) as a near market comparator. The submission stated (p22) that the trials used to gain TGA approval for Oriprio were not specific to Oriprio. The submission provided no further discussion of Oriprio as a near market comparator. Oriprio was also considered at the November 2020 PBAC Meeting for the same PBS population.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the clinical evidence available to support the effectiveness of progesterone in preventing pre-term birth, and presented information about the use of progesterone in practice.
- 6.2 The PBAC considered that the hearing was informative as it provided a clinical perspective on preventing pre-term birth.
- 6.3 The PBAC noted that the clinician referred to prevention of miscarriage in women with a history of repeated miscarriage, although this indication does not fall within the requested population.

Consumer comments

- 6.4 The PBAC noted that no consumer comments were received for this item.
- 6.5 The PBAC noted that consumer comments were received for Oriprio and are included in the Public Summary Document (PSD) for Oriprio.

Clinical trials

6.6 The submission included two clinical trials (UTRO-200-PTD and Fonseca 2007) and one meta-analysis (Romero 2018). The clinical claim and economic evaluation were based on data from the Romero (2018) meta-analysis.

6.7 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and meta-analyses presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
UTRO-200-PTD/MISTERI	Multinational, multicentre, open-label, parallel group trial to evaluate efficacy and safety of micronized progesterone (vaginal capsules) in high risk for preterm delivery women.	June 2014
Fonseca 2007	Fonseca EB, Celik E et al. Progesterone and the risk of preterm birth among women with a short cervix.	NEJM 2007; 357 462-469.
Romero 2018	Romero R, Conde-Agudelo A et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data.	Am J Obstet Gynecol 2018; 218(2): 161-180.

Source: Table 2.5, p39 of the submission.

6.8 While the literature searches were satisfactory in that relevant trials and meta-analyses were identified, the searches did not identify additional publications that were potentially also relevant, such as a 2019 NICE evidence review² of the clinical effectiveness of progesterone for prevention of preterm labour and birth, a Cochrane overview of systematic reviews of interventions to prevent preterm birth (Medley 2018³), as well as additional reviews and discussion of the use of progesterone in pregnancy (e.g. Prior 2017⁴). The ESC considered that these reviews supported the clinical claim for progesterone for the requested PBS population. The ESC noted that the Patient-Centered Outcomes Research Institute (PCORI) is undertaking a large, individual level meta-analysis⁵, which should provide more definitive evidence for the effectiveness of progesterone in preterm birth.

6.9 The key features of the randomised trials and meta-analysis are summarised in the table below.

² NICE guideline NG25 2019: Preterm labour and birth [A] Evidence review for clinical effectiveness of prophylactic progesterone in preventing preterm labour. Available at:

<https://www.nice.org.uk/guidance/ng25/evidence/a-clinical-effectiveness-of-prophylactic-progesterone-in-preventing-preterm-labour-pdf-6847804765>

³ Medley N, Vogel JP, Care A, Alfirevic Z. Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev* 2018; Issue 11: Art. No. CD012505. DOI: 10.1002/14651858.CD012505.pub2.

⁴ Prior M, Hibberd R, Asemota N, Thornton JG. Inadvertent P-hacking among trials and systematic reviews of the effect of progestogens in pregnancy? A systematic review and meta-analysis. *BJOG* 2017; 124: 1008-1015.

⁵ Norman, J.E. Progesterone and preterm birth. *Int J Gynaecol Obstet* 2020; 150: 24-30.

Table 3: Key features of the included evidence

Trial	N	Design/ location	Risk of bias	Study population	Outcome(s)	Use in cost analysis
UTRO-200-PTD	Progesterone 200 mg: N=220	OL, MC Russia, Ukraine, Belarus	High	Short cervix <25 mm; history of preterm birth	Preterm delivery <34 weeks	No
Fonseca 2007	Progesterone 200 mg: N=125 SOC: N=125 Total: N=250	R, DB, MC UK, Chile, Brazil, Greece	Low	Short cervix ≤15 mm	Preterm delivery <34 weeks	No
Romero 2018	Progesterone 90-200 mg: N=498 SOC: N=476 Total: N=974 from 5 trials: Fonseca 2007, O'Brien 2007, Hassan 2011, Cetingoz 2011, Norman 2016	IPD meta-analysis UK, Chile, Brazil, Greece, US, South Africa, India, Czech Republic, Chile, El Salvador, Turkey, Belarus, Israel, Italy, Russia, Ukraine, Sweden	Low	Singleton or twin pregnancy, cervical length <25 mm	Preterm delivery <33 weeks	Yes

Source: Table 2.8, p47; Table 2.9, p49; Table 2.56, p92-93 of the submission.

DB=double blind; IPD=individual participant data; MC=multi-centre; OL=open label; R=randomised; SOC=standard of care

- 6.10 The UTRO-200-PTD trial recruited women in Russia, Ukraine and Belarus. It was an open-label, non-comparative trial including women with a short cervix (>10 mm and <25 mm) or a history of preterm birth. The trial was considered to have a high risk of bias as it was not blinded, although the objective outcomes assessed in the trial minimised the risk of bias. Results of the trial were not used as part of the cost analysis.
- 6.11 The Romero (2018) meta-analysis was based on five trials (Fonseca 2007; O'Brien 2007; Hassan 2011; Cetingoz 2011; Norman 2016). Women in these trials had cervical length <25 mm and/or a history of preterm birth. Two of the trials (Fonseca 2007 and Cetingoz 2011) included twin pregnancies. The submission did not provide any discussion on the impact this may have on the applicability of the Romero (2018) meta-analysis to the proposed PBS population, which is for singleton pregnancies only.
- 6.12 The submission provided justification for exclusion of two trials (Norman 2016; van Os 2015) and three meta-analyses (Dodd 2013; Romero 2016; Jarde 2017). The exclusion of the meta-analyses was reasonable, as the Romero (2018) analysis included many of the same trials assessed in the other meta-analyses. However, the ESC noted Jarde 2017 concluded that for women with either a prior preterm birth or a shortened cervix, progesterone was effective: "Vaginal progesterone was the only intervention with consistent effectiveness for preventing preterm birth in singleton at risk pregnancies overall and in those with a previous preterm birth".
- 6.13 The submission did not identify an overview of Cochrane systematic reviews (Medley 2018, paragraph 6.5), which described 83 systematic reviews assessing ways to prevent preterm birth, of which 70 have outcome data. Of the 70 reviews, 36 were reviews of interventions with the aim of preventing preterm birth, including cervical cerclage, midwife-led models of care and zinc supplementation. The ESC noted that much of these outcome data were not relevant to the submission.

- 6.14 A systematic review and meta-analysis by Prior 2017, also not identified in the submission (paragraph 6.5), discussed that earlier studies and reviews may have been biased by either selective publication or selective choice of outcome. The Prior 2017 paper presented a meta-analysis assessing preterm birth using only trials that were registered (in publicly available trial registries recognised by the WHO⁶) and reported predefined primary outcomes, i.e. at less risk of bias due to selective publication or selective choice of outcome. This analysis included eight trials and found no advantage for progesterone in preventing preterm birth prior to 34 weeks (RR=0.90; 95% CI: 0.77, 1.06), and had an I² value of 33%, indicating some heterogeneity. However, the analysis included trials that used intramuscular progestogens, and was not exclusive to vaginal progestogens.
- 6.15 Only three of the trials included in the Romero (2018) meta-analysis were registered (in WHO-recognised publicly registered trial registries⁶) and used predefined primary outcomes (O'Brien 2007; Hassan 2011; Norman 2016).

Comparative effectiveness

UTRO-200-PTD

- 6.16 The table below summarises the key results from UTRO-200-PTD for prevention of preterm birth compared to preterm birth population risk in literature data.

Table 4: Occurrence of preterm birth (<34 weeks) in UTRO-200-PTD in comparison to literature data

Assessment group	RR (95% CI)	RRR (95% CI)	NNT (95% CI)
Cervical shortening (N=109)	0.22 (0.1, 0.48)	0.8 (0.52, 0.9)	5 (4, 8)
Medical history (N=110)	0.22 (0.1, 0.48)	0.8 (0.52, 0.9)	5 (4, 8)
Total group (N=219)	0.22 (0.12, 0.4)	0.78 (0.61, 0.88)	5 (4, 7)

Source: Table 2.22, p70 of the submission.

CI=confidence interval; NNT=number needed to treat; RR=relative risk; RRR=relative risk reduction; **bold**=statistically significant

- 6.17 The submission claimed (p71) that the risk of preterm birth to 34 weeks was reduced in all groups in the trial, with statistically significant risk reductions observed. The relative risk and relative risk reduction calculated for women enrolled in UTRO-200-PTD (all women received Utrogestan) was based on a comparison with a literature population. Neither the submission nor the clinical study report (CSR) provided any information on this population, and the rates of preterm birth used, although the CSR stated (p46) that the preterm birth population risk is at least 25% according to literature data. Hence, the reported differences were difficult to interpret.

Fonseca 2007

- 6.18 The submission reported that the rate for the primary outcome, spontaneous birth <34 weeks of gestation, was significantly reduced in the progesterone group (19.2%) compared to the SOC group (34.4%) (RR=0.56; 95% CI: 0.36, 0.86). For singleton pregnancies, the incidence of preterm birth was 17.5% for women treated with

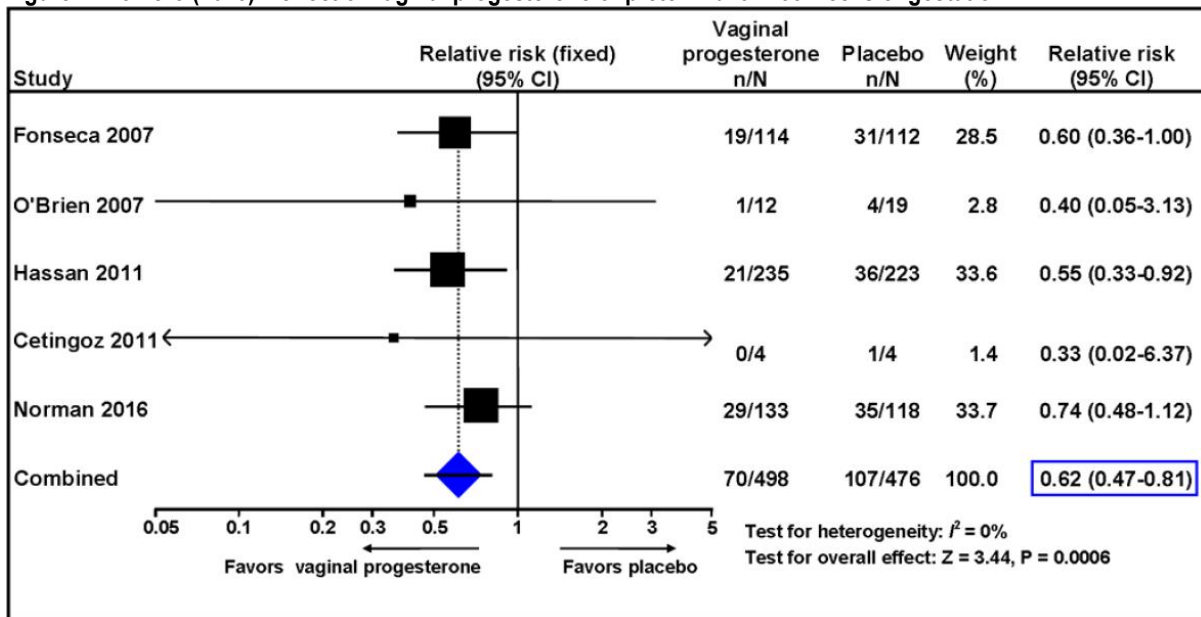
⁶ WHO International Clinical Trials Registry Platform is available at: <https://www.who.int/ictpr/network/primary/en/>

progesterone compared to 32.1% for women treated with SOC (RR=0.54; 95% CI: 0.34, 0.88).

Romero 2018

6.19 The primary outcome in the Romero (2018) meta-analysis was risk of preterm birth at <33 weeks. The results for the key analysis are provided in the forest plot below.

Figure 1: Romero (2018) – effect of vaginal progesterone of preterm birth <33 weeks of gestation



Source: Figure 2.6, p98 of the submission.

6.20 The analysis showed that vaginal progesterone statistically significantly reduced the risk of preterm birth at <33 weeks gestation (14%) compared to SOC (22%), with RR=0.62; 95% CI: 0.47, 0.81. The meta-analysis had an I^2 value of 0%, suggesting that heterogeneity may not be an issue.

6.21 For the primary outcome of the meta-analysis (preterm birth at <33 weeks) only one trial showed an advantage for progesterone (Hassan 2011), three of the trials showed no advantage for progesterone (O'Brien 2007; Cetingoz 2011; Norman 2016) and one trial had a borderline advantage (Fonseca 2007⁷). The ESC noted that only a subset of the population reported in the Norman 2016 study met the proposed PBS criteria.⁸

6.22 The ESC considered that overall the results of the meta-analysis should be interpreted with caution given the comments in Prior (2017) relating to selection and reporting bias, and the trials included in Romero (2018).

⁷ The numbers reported for Fonseca (2007) in the Romero (2018) meta-analysis differ from those reported in the Fonseca (2007) publication. There is no information available as to why these numbers differ.

⁸ In the Norman 2016 study, women at risk of preterm birth comprised those with previous spontaneous birth at ≤ 34 weeks and 0 days of gestation, or a cervical length ≤ 25 mm, or a positive foetal fibronectin test combined with other clinical risk factors for preterm birth (any one of a history in a previous pregnancy of preterm birth, second trimester loss, preterm premature fetal membrane rupture, or a history of a cervical procedure to treat abnormal smears).

Comparative harms

- 6.23 The submission presented adverse event (AE) data from the UTRO-200-PTD trial, although the data presented was based on indications for caesarean section and postpartum outcomes. The submission reported that 110 women (50%) experienced at least one AE during the trial and there were six serious AEs reported: walking pneumonia, gestosis, foetal growth retardation, threatened preterm birth, premature discharge of amniotic fluid, and pruritus gravidarum.
- 6.24 The Fonseca (2007) trial reported there were no important AEs or side effects in the progesterone or placebo (SOC) groups. None of the women reported an increase in frequency or severity of general or local side effects, such as sleepiness, fatigue, headaches or genital irritation, or any new symptoms after the onset of treatment. The Fonseca (2007) publication did not provide any numerical data on the occurrence of AEs and it was difficult to draw any conclusions on the safety of Utrogestan on the basis of this report.
- 6.25 The Romero (2018) meta-analysis showed no statistically significant difference between the progesterone and SOC groups for the occurrence of any maternal adverse event (RR=1.21; 95% CI: 0.87, 1.69). Respiratory distress syndrome in newborns was significantly reduced where mothers had received progesterone during pregnancy (RR=0.47; 95% CI: 0.27, 0.81).
- 6.26 The submission noted that post-marketing information indicated that the frequency of vaginal haemorrhage, vaginal discharge and drug intolerance was not known, as it could not be estimated from the available data. Thus, the only available information for these outcomes was the trial data, and that presented by the submission showed one case of vaginal discharge between visit 1 and 2 for Utrogestan-treated women in the UTRO-200-PTD trial (0.45%), and neither the Fonseca (2007) trial or the Romero (2018) meta-analysis reported vaginal discharge. Hence, there was no information provided by the submission regarding the AE of vaginal discharge.
- 6.27 The ESC considered that overall, progesterone appeared to be well tolerated with no major safety concerns.

Benefits/harms

- 6.28 A summary of the comparative benefits and harms for progesterone versus SOC is presented in the table below.

Table 5: Summary of comparative benefits and harms for progesterone and SOC

Trial	Progesterone n/N	SOC n/N	RR (95% CI)	Event rate/100 women	
				Progesterone n/N	SOC n/N
Benefits					
Preterm birth <33 weeks					
Romero 2018 meta-analysis (I ² =0%)	70/498	107/476	0.62 (0.47, 0.81)	14.1	22.5
Harms					
Maternal adverse events					
Romero 2018 meta-analysis (I ² =5%)	51/424	47/422	1.21 (0.87, 1.69)	12.0	11.1

Source: Figure 2.6, p98; Table 2.59 p98-99 of the submission

RR=relative risk; SOC=standard of care; **bold**=statistically significant

^a Treatment duration ranged from 10 to 19 weeks in the five trials included in the Romero (2018) meta-analysis.

6.29 On the basis of meta-analysis evidence presented by the submission, for every 100 women treated with progesterone in comparison with SOC for a treatment period of 10 to 19 weeks:

- There would be approximately 8 fewer preterm births (defined as birth prior to 33 weeks gestation).
- There would be no difference in maternal adverse events between those treated with progesterone and those treated with SOC.

6.30 The ESC noted a significant reduction in the number of preterm births and no difference in harms.

Clinical claim

6.31 The submission described progesterone (Utrogestan) as superior in terms of effectiveness compared with SOC and as having acceptable safety.

6.32 The PBAC noted that the clinical evidence was of variable quality and applicability to the proposed PBS population.

6.33 The PBAC considered that while the claim of acceptable safety was based on limited evidence, adverse effects appeared to be minimal. The PBAC considered that the claim of non-inferior safety was reasonable.

6.34 The PBAC considered that while the sponsor may have overstated the benefit of progesterone, on balance it was reasonable to accept that progesterone is associated with a risk reduction in preterm birth.

6.35 The PBAC noted that there is consistent recommendation of progesterone for the prevention of preterm birth in clinical guidelines.

Economic analysis

6.36 The submission presented a modified economic evaluation, consisting of a trial-based evaluation, and a cost analysis, comparing one group of women who receive Utrogestan treatment, and a second group who do not receive Utrogestan, assessing neonatal hospitalisations and neonatal morbidity to one year.

6.37 The modified economic evaluation was based on the submission’s claim that Utrogestan had superior efficacy and non-inferior safety compared to SOC in the prevention of preterm birth.

6.38 The table below outlines the key aspects of the cost analysis presented.

Table 6: Key components of the modified economic evaluation

Component	Description	Justification/comments
Type of analysis	Trial-based analysis Cost analysis	Appropriate.
Outcomes	Neonatal hospitalisations, neonatal morbidity	Reasonable, although subsequent costs (and benefits) associated with more infants who are alive is not included.
Time horizon	Trial-based analysis: 16 weeks Cost analysis: 1 year	Reasonable.
Methods used to generate results	Preterm birth from Romero (2018) with hospitalisation costs applied by gestational age.	May not accurately reflect all of the available evidence.
Key assumptions and components of the economic evaluation as presented by the submission		
Component	Claim or assumption	Justification/comments
Therapeutic claim: effectiveness	Effectiveness is assumed to be superior.	Based on the Romero (2018) meta-analysis which may not have included all relevant studies.
Therapeutic claim: safety	Safety is assumed to be non-inferior.	Reasonable.
Direct medicine costs	\$ [REDACTED]	Assumes 100% compliance which was not reflected in the clinical trials. Also assumes use of a partial pack, however women will not obtain 0.67 of a script so cost is underestimated. The ESC considered the cost of progesterone should have been based on 3 full packs rather than 2.67 packs.
Other costs or cost offsets	Fewer hospitalisations due to preterm birth.	Relies solely on Romero (2018) data.

Source: Table 3.1, p133; Section 3.1.3, p135 of the submission.

6.39 Table 7 outlines the costs applied in the trial-based and cost analyses.

Table 7: Costs applied in the trial-based and cost analyses

Component	Cost	Description
Utrogestan	\$ [REDACTED]	Cost of course of treatment, based on assumed treatment duration of 16 weeks (2.67 packs) and full compliance. Applied in trial-based and cost analyses.
Preterm hospitalisation	\$28,752	Weighted cost for all AR-DRG's for neonatal care in 2016-2017. Applied to trial-based evaluation only.
<37 weeks	\$22,679	Weighted AR-DRG costs from 2016-2017 indexed to 2021 values (assumed time of listing) using assumed inflation of 2% per annum. Applied in cost analysis.
<36 weeks	\$22,679	
<35 weeks	\$18,359	
<34 weeks	\$18,359	
<32 weeks	\$37,299	
<30 weeks	\$84,137	
<28 weeks	\$206,838	
Full-term birth	\$3,082	Value of \$2,430 sourced from Lain (2013) inflated to 2020 values. Applied in cost analysis.
Hospitalisation with neonatal morbidity	\$5,195	Sourced from Lain (2013) which described cost of morbidity based on whether neonatal morbidity existed. Costs were inflated to 2020 values. Applied in cost analysis.
Hospitalisation without neonatal morbidity	\$1,111	

Source: Excel workbook 'Besins Utrogestan in PTB PBAC Major Submission July 2020 – Section 3 Workbook'.

6.40 Table 8 presents the results of the trial-based analysis.

Table 8: Results of the trial-based analysis

Component	Value
Utrogestan cost per course	\$ [REDACTED]
NNT	12
Cost of Utrogestan to avoid one preterm birth and a neonatal admission	\$ [REDACTED] (\$ [REDACTED] x [REDACTED])
Weighted average cost for one neonatal hospital admission	\$ [REDACTED]
Cost impact per 12 pregnancies	-\$ [REDACTED]
Cost impact per pregnancy	-\$ [REDACTED]

Source: Table 3.2, p134 of the submission; Excel workbook 'Besins Utrogestan in PTB PBAC Major Submission July 2020 – Section 3 Workbook'.

NNT=number needed to treat

6.41 Table 9 presents the results of the cost analysis.

Table 9: Results of the cost analysis

Component	Cohort of one woman		
	Utrogestan	SOC	Increment
Effectiveness inputs (sourced from Romero 2018)			
Rate of pre-term birth <33 weeks	14.06%	22.48%	-
Number of pre-term births	0.14	0.22	-0.08
Number of full-term births	0.86	0.78	0.08
Drug cost (2.67 packs; \$ [REDACTED] / [REDACTED])	\$ [REDACTED]	\$0	\$ [REDACTED]
Neonatal hospitalisation cost			
Pre-term births			
<37 weeks (\$22,679 per admission)	\$818	\$845	-\$27
<36 weeks (\$22,679 per admission)	\$563	\$640	-\$78
<35 weeks (\$18,359 per admission)	\$276	\$311	-\$35
<34 weeks (\$18,359 per admission)	\$331	\$705	-\$374
<32 weeks (\$37,299 per admission)	\$364	\$1,053	-\$689
<30 weeks (\$84,137 per admission)	\$696	\$1,236	-\$540
<28 weeks (\$206,838 per admission)	\$5,908	\$12,617	-\$6,709
Total pre-term births	\$8,956	\$17,408	-\$8,451
Full-term births (\$3,082 per admission)	\$2,649	\$2,389	\$260
Total	\$11,605	\$19,797	-\$8,192
Morbidity years 0 to 1 (hospitalisation without neonatal morbidity \$1,111; hospitalisation with neonatal morbidity \$5,195)	\$1,685	\$2,029	-\$344
Total cost impact	\$ [REDACTED]	\$21,826	-\$ [REDACTED]

Source: Table 3.6, p138 of the submission; Excel workbook 'Besins Utrogestan in PTB PBAC Major Submission July 2020 – Section 3 Workbook'.

SOC=standard of care

6.42 The cost analysis resulted in a saving of \$0 to <\$10M with the use of Utrogestan for the prevention of preterm birth. The saving estimated by the submission relied on the efficacy observed in the Romero (2018) meta-analysis. The ESC noted the 8% difference in the number of pre-term births was validated in the submission based on the outcomes of the Whole 9 Months, a public health and social media campaign of the Western Australian Preterm Birth Prevention Initiative and the Australian Preterm Birth Prevention Alliance, which aimed to safely lower the rate of preterm birth by combining the latest evidence-based clinical practice with educational outreach programs for health care practitioners and the general public. The ESC noted the WA

study included a number of management changes in addition to use of progesterone and hence the results do not reflect the impact of progesterone alone. The ESC further noted that the initial gains from the WA initiative, in terms of reducing pre-term births, were not uniformly maintained across different health care settings⁹.

- 6.43 The ESC noted that the cost differences were largely driven by the reduction in the number of births prior to 28 weeks. However, a reduction in preterm births <28 weeks was not observed in meta-analyses other than Romero 2018, therefore this benefit may not be realised.
- 6.44 The ESC noted that costs applied to pre-term births, and in particular the cost applied to births prior to 28 week (\$202,838 per admission), were high and included (weighted by separations) AR DRG costs for admissions involving significant operating room procedures and admissions with major complexities. The ESC considered that, given the main clinical evidence did not report birthweight (and hospital costs are based on birthweight¹⁰) the available evidence may not support a reduction in pre-term births at the levels of admission complexity assumed, thus it is very uncertain whether the assumed AR DRG costs would be relevant to the PBS population.
- 6.45 The ESC noted that the model applied the cost of neonatal hospitalisation to all births prior to full term, however considered that not all births after 28 weeks would require neonatal hospitalisation. Therefore, the savings were likely overestimated.
- 6.46 The ESC noted no difference in background treatment costs (e.g. ultrasounds, maternal care) was assumed for the SOC and Utrogestan treatment groups.
- 6.47 The ESC noted that the model did not consider the finding that progesterone may be associated with an infant mortality benefit.
- 6.48 Overall the ESC considered the reduction in pre-term births and the hospitalisation costs assumed in the cost analysis to be very uncertain. However the ESC also acknowledged that the cost of progesterone per pregnancy was small in comparison to the potential saving from hospital admissions for pre-term births.

Drug cost/pregnancy

Table 10: Drug cost per pregnancy for Utrogestan

	Utrogestan		
	Trial dose and duration	Cost analysis	Financial estimates
Mean dose	200 mg/day	200 mg/day	200 mg/day
Mean duration	10 weeks to 19 weeks	16 weeks	16 weeks
Cost/pregnancy	\$ [redacted] to \$ [redacted] ^a	\$ [redacted] ^b	\$ [redacted] ^b

Source: Table 3.2, p134 Italicised values have been calculated.

^a Trial-based cost used partial pack sizes, as did the submission for the cost analysis and financial estimates.

^b The submission assumed 2.67 packs will be required per course (16 weeks=112 days; 1 pack=42 days).

⁹ Newnham et. al. The elements of success in a comprehensive state-wide program to safely reduce the rate of preterm birth, *PLOS ONE* 2020; DOI: 10.1371/journal.pone.0234033.

¹⁰ The submission identified a study by Dobbins (2012) which provided Australian national birthweight percentiles by gender and gestational age for 2.5M singleton births between 1998 to 2007.

6.49 Both the cost analysis and financial estimates assumed that 16 weeks of treatment (112 days) would require 2.67 packs of Utrogestan (1 pack=42 days). However, 0.67 of a pack would not be able to be obtained and an additional pack would need to be prescribed to obtain the required number of capsules. As such, the costs are underestimated.

Estimated PBS usage & financial implications

6.50 The submission was considered by DUSC.

6.51 The submission applied an epidemiological approach to develop the financial estimates, based largely on AIHW data, along with literature-based estimates for the proportion of women with cervical length <25 mm and a history of preterm birth (Table 11).

Table 11: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalence data	ABS data: Number of females that give birth 2021 to 2026, using ABS 3222.0 Series B. AIHW data: Proportion of singleton births: 98.53%.	Assumption that the birth rate will not change over 6 years was not likely to be accurate.
Proportion with cervical length ≤25 mm	Salomon 2009: cervical length <25 mm: 1.92% of pregnant women at 16-24 weeks of gestation.	Of the 6,614 cervical length measurements in Salomon (2009), there were 653 women with cervical length <25 mm (9.8%), and there was significant non-normality and significant negative skew. The submission did not address this non-normality and skew and instead applied an average of proportions observed between 16 and 36 weeks. This is not likely to provide an accurate estimate of the proportion of women with cervical length ≤25 mm. In addition, the clinical trials analysed in the Romero (2018) meta-analysis showed higher proportions, such as 10% in Fonseca (2007) and 36% in Norman (2016).
Proportion with history of preterm birth	Koullali 2020: rate of prior preterm birth 1.58% with a multiplier of 1.59 resulted in a rate of 2.51%.	2.51% was likely to be an underestimate and is considerably less than the 8.6% based on AIHW data, and may not apply to the entire proposed PBS population, as it was based only on women with a second pregnancy who had a prior preterm birth.
Uptake rate	Sponsor assumption: 70% in Year 1, 71% in Year 2, 72% in Year 3, 73% in Year 4, 74% in Year 5, 75% in Year 6.	Reasonable.
Treatment duration	16 weeks	Does not correspond to trial data nor to potential use for up to 24 weeks (16 weeks to 40 weeks) (para 3.1).
Compliance rate	100%	Does not correspond to trial data, which ranged from 66% to 100%, with most trials around 90%.
Grandfathered clients	Not included.	Reasonable.
Dose/duration	200 mg/day from 16-24 weeks of gestation to 36 weeks or until delivery.	The economic evaluation and financial estimates assumed 16 weeks of treatment, however treatment could be up to 20-24 weeks (para 3.1).
MBS items	Not included.	Underestimated the financial implications.

Source: Section 4.1 to 4.5, p141-151 of the submission.

ABS=Australian Bureau of Statistics; AIHW=Australian Institute of Health and Welfare

6.52 The sponsor estimated number of pregnancies, script numbers and costs for the PBS listing of Utrogestan are provided below.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number initiating treatment	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed ^a	█ ²	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Estimated financial implications of Utrogestan						
Cost to PBS/RPBS	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Co-payments	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³
Net cost to PBS/RPBS	\$█³	\$█³	\$█³	\$█³	\$█³	\$█³

Source: Table 4.11, p147 of the submission.

^a Assuming 2.67 packs per patient per course of treatment as estimated by the submission.

The redacted values correspond to the following ranges:

¹5000 to <10,000

²10,000 to <20,000

³\$0 to <\$10 million

⁴20,000 to <30,000

6.53 The net cost to Government was estimated to be \$0 to <\$10M in Year 6, and a total of \$0 to <\$10M in the first 6 years of listing.

6.54 Australian Institute of Health and Welfare (AIHW) data was used to estimate the number of women who would give birth in Year 1 through Year 6 (58.3 per 1000). The submission assumed the rate remained the same over the first 6 years of listing. DUSC considered it would have been more informative to use a linear trend based on AIHW data to estimate the birth rate over the forward estimates period.

6.55 The submission calculated the average proportion of women between 16 and 24 weeks gestation with cervical length ≤25 mm as 1.92% based on data from Salomon (2009). DUSC considered that while it was inappropriate to calculate the average proportion in this way Temming et al. also estimated 2% of women had cervical length <25mm when screened between 17 and 23 weeks.

6.56 The proportion of singleton pregnancies with prior preterm births was calculated to be 2.51%. This proportion was sourced from Koullali (2020), which was a retrospective study assessing live singleton births of 802,119 pregnancies in the Netherlands. The paper reported that of the 289,391 second pregnancies, 1.5% of mothers had a prior preterm birth. The proportion was 1.7% for the third birth, 2.0% for the fourth birth and 2.1% for the fifth birth. The submission calculated a weighted average across the births of 1.58%, which the submission stated means 1.58% of women with their second pregnancy have a history of preterm birth and would be eligible for Utrogestan. The submission added this may be an underestimate as the Koullali (2020) study was based on women in the Netherlands and reported an incidence of preterm birth of 5.4%, versus the rate of 8.6% in Australia, based on AIHW data. The submission therefore applied a multiplier of 1.59 (8.6/5.4) to increase the proportion at risk of preterm birth and be representative of an Australian population. DUSC considered

that the proportion of patients with preterm birth may have been underestimated. DUSC noted other higher proportions reported in the literature, such as 5.72% from Yang (2016). The sponsor disagreed with DUSC's calculation of the eligible patient population (pre-PBAC response). The sponsor claimed that the methodology used by DUSC was for all pre-term births, not the proportion of pregnant women who have had a previous pre-term birth.

- 6.57 DUSC noted that script numbers are impacted by the assumption that a treatment course will be 16 weeks, and patients will have full compliance.
- 6.58 Overall, DUSC considered the patient numbers were not likely to be accurately estimated. As cervical length and history of preterm birth were the key defining characteristics of the proposed restriction, the low proportions used by the submission resulted in likely underestimation of the eligible and initiating treatment populations. DUSC considered the script numbers were also likely to be underestimated, and were further impacted by the assumption that a treatment course would be 16 weeks, and patients would have full compliance.
- 6.59 DUSC considered that for the purposes of deriving the utilisation estimates, the population should be defined as women with a singleton pregnancy with a history of spontaneous (preterm) birth or who have a short cervix (midtrimester ≤ 25 mm). Based on this definition, DUSC proposed the following method to estimate the eligible population (Table 13).

Table 13: DUSC estimated eligible population

Model step	Parameter description	Input	Comment
[1]	Females 15-44 years	5,394,983	
[2]	Percentage of pregnant women	5.83%	AIHW 2018, 58.3 per 1000
[3] = [1] x [2]	Number of pregnant women aged 15-44 years	314,528	
[4]	Proportion of pregnancies with a singleton birth	98.52%	AIHW 2018 data. 303,029 babies born to 298,630 mothers. The resultant proportion of singleton births was 98.53% $(1-(303,029-298,630)/298,630)$.
[5] = [3] x [4]	Number of women with singleton birth	309,873	
Population 1 - First pregnancy, singleton birth, short cervix			
[6]	Proportion of women with first pregnancy	42.0%	Pregnancy outcome in South Australia 2017', Pregnancy Outcome Unit October 2019 Wellbeing SA p.12. Accessed at: https://www.sahealth.sa.gov.au
[7]	Proportion of women with cervix ≤ 25 mm	2%	Temming et al. Universal Cervical Length Screening: Implementation and Outcomes. Am J Obstet Gynecol. 2016 April ; 214(4): 523.e1–523.e8
[8] = [5]x[6]x[7]	First pregnancy, singleton birth, short cervix	2,603	
Population 2 - Prior pregnancy, singleton birth, short cervix			
[9]	Proportion of women with prior pregnancy	58.0%	'Pregnancy outcome in South Australia 2017', Pregnancy Outcome Unit October 2019 Wellbeing SA p.12. Accessed at: https://www.sahealth.sa.gov.au
[10] = [5]x[9]x[7]	Prior pregnancy, singleton birth, short cervix	3,595	
Population 3 - Prior pregnancy, prior pre-term birth			
[11]	Prior pre-term birth rate	7.0%	Withanawasam and Tara (2019). The shortened cervix in pregnancy Investigation and current management recommendations for primary caregivers. AJGP (48(3): 121-123.
[12] = [5]x[9]x[11]	Prior pregnancy, singleton birth, prior pre-term birth	12,581	
[13] = [8]+[10]+[12]	Total eligible population	18,778	

6.60 The submission stated (p152) that due to the low cost per treatment course and the low net impact to Government, the sponsor did not consider a risk-sharing

arrangement was necessary. DUSC noted that the projected financial implications relied on the assumed low proportions of patients with cervical length ≤ 25 mm (1.92%) and prior preterm birth (2.51%). DUSC considered that these assumptions were likely to be underestimated and the potential costs of listing progesterone were likely to be greater than estimated by the submission. The PBAC considered that the number of women seeking preventative treatment with progesterone remained highly uncertain, there was a high risk of leakage to women who are lower risk, and that an Authority Required (STREAMLINED) listing is a low barrier to accessing treatment. Therefore the PBAC advised that a RSA would be required.

- 6.61 The DUSC noted there was the potential of off-label use of progesterone in repeated first term miscarriage. The sponsor contended that the restriction criteria and Authority Required (STREAMLINED) listing would mitigate this risk. The PBAC noted that a Cochrane review¹¹ suggested progesterone may be beneficial in preventing miscarriage in women with a history of repeated miscarriage, and noted comments made by the clinician in the sponsor hearing about use for this indication (paragraph 6.3). The PBAC considered that additional criteria that initiation must not be prior to 16 weeks gestation (paragraph 3.3) would help mitigate the risk of off-label, non-PBS subsidised use as miscarriage prophylaxis.

Quality Use of Medicines

- 6.62 The risk management plan listed important identified risks as gravidic cholestasis, ovarian cancer and breast cancer, and the submission noted that the risk minimisation measures have been confirmed as effective.
- 6.63 The ESC noted that patient adherence is an important consideration with progesterone use, because a drop in progesterone can trigger the commencement of labour. The ESC emphasised that while this is a theoretical issue with no associated clinical data available, the prescribing of progesterone should be part of a comprehensive support program.
- 6.64 DUSC commented that, in addition to educating patients and prescribers about progesterone use, significant risk factors associated with pre-term birth should also be raised, including: the additional risks of previous pre-term birth; social disadvantage; lower levels of maternal education; pre-existing or gestational diabetes; urogenital infection; alcohol consumption; and smoking.

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

¹¹ Haas DM, Hathaway TJ, Ramsey PS. Progesterone for preventing miscarriage in women with recurrent miscarriage of unclear etiology. Cochrane Database of Systematic Reviews 2019, Issue 11. Art. No.: CD003511. DOI: 10.1002/14651858.CD003511.pub5

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of progesterone (Utrogestan) for the prevention of preterm birth in women with singleton pregnancies and a short cervix (≤ 25 mm) and/or a history of preterm birth.
- 7.2 The PBAC was satisfied that Utrogestan provides, for some women, a significant improvement in efficacy over standard of care (SOC). The PBAC noted the submission included cervical cerclage as an example of SOC.
- 7.3 The PBAC noted that there are no other pharmacological treatments prescribed to reduce the risk of preterm birth, and that there is a clinical need for interventions for the prevention of preterm birth in at-risk women.
- 7.4 The PBAC noted that the use of progesterone was consistent with international and RANZCOG clinical guidelines, and recognised that access to progesterone should be equitable for all women in the target population. The PBAC noted that currently, women being treated outside the public hospital system or in a remote location can only access progesterone through a private script. The PBAC noted that preterm birth is associated with vulnerable populations with comorbidities, Aboriginal/Torres Strait Islander descent or socio-economic disadvantage.
- 7.5 The PBAC considered that the restriction should specify:
- It must be a singleton pregnancy
 - Patient must have at least one of either: (1) a short cervix (mid-trimester cervix ≤ 25 mm) or (ii) must have a history of spontaneous preterm birth
 - Treatment must not be commenced prior to 16 weeks gestation
 - No increase in the maximum quantity or number of units may be authorised
 - No increase in the maximum number of repeats may be authorised
- 7.6 The PBAC considered that the proposed restriction criteria “patient must be pregnant” was not required.
- 7.7 The PBAC considered the nominated comparator, SOC, to be appropriate and considered that Oriprio (progesterone) was a near market comparator.
- 7.8 The PBAC noted that the clinical evidence was of variable quality and applicability to the proposed PBS population. The PBAC noted that overall the evidence supported a statistically significant reduction in pre-term birth prior to 33 weeks gestation. The PBAC considered that it was reasonable to accept that progesterone is associated with a risk reduction in preterm birth.
- 7.9 The PBAC noted that there was limited evidence to support the claim of acceptable safety, however considered the claim of non-inferior safety versus SOC was reasonable.
- 7.10 The PBAC noted that the reduction in pre-term births and the hospitalisation costs assumed in the cost analysis were very uncertain. However, the PBAC also noted that

the cost of progesterone per pregnancy was small in comparison to the potential saving from hospital admissions for pre-term births, and considered Utrogestan to be acceptably cost-effective at the price proposed in the submission.

- 7.11 The PBAC considered that the estimated utilisation of progesterone was highly uncertain, and could be addressed by a risk sharing arrangement (RSA). The PBAC considered that the population estimates presented by DUSC were the most reasonable, and that the estimates should be revised to align with the DUSC estimates. The PBAC advised that the RSA should be based on the DUSC estimates. The PBAC considered that the cost per pregnancy may be greater than the estimate, which assumed use for 16 weeks, as treatment could continue for up to 24 weeks.
- 7.12 The PBAC considered that an utilisation review by DUSC should be conducted two years after initial listing.
- 7.13 The PBAC considered that educating women and prescribers about progesterone use would be important, and further noted additional risk factors that should be raised including: previous pre-term birth; social disadvantages, lower levels of maternal education; pre-existing or gestational diabetes; urogenital infection; alcohol consumption and smoking.
- 7.14 The PBAC advised that progesterone is suitable for prescribing by nurse practitioners and midwives for the prevention of preterm birth. The PBAC considered that this would support access to treatment for women in regional and remote areas
- 7.15 The PBAC recommended that the Early Supply Rule should not apply.
- 7.16 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for progesterone:
- a) the treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over standard of care. The PBAC considered this criteria was not met as the available evidence was of variable quality and applicability to the proposed PBS population;
 - b) The treatment is not expected to address a high and urgent unmet clinical need;
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.17 The PBAC noted that this submission was not eligible for an Independent Review, as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Add new item as follows:

MEDICINAL PRODCUT, medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
PROGESTERONE progesterone 200 mg capsule, 42	NEW	1	42	3	Utrogestan

Restriction Summary [new RS1] / Treatment of Concept: [new ToC1]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Midwives
Restriction Type – <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
Episodicity: Prevention of
Severity: [blank]
Condition: preterm birth
Indication: Prevention of preterm birth
Clinical criteria: Patient must have a singleton pregnancy
AND
Clinical criteria: Patient must have at least one of: (i) short cervix (mid-trimester sonographic cervix no greater than 25 mm), (ii) a history of spontaneous preterm birth
AND
Clinical criteria: The treatment must be administered no earlier than at 16 weeks gestation
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.

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 welcomes the PBAC's decision to recommend Utrogestan for the prevention of preterm birth.