6.10 PROGESTERONE, Pessary 200 mg, Oripro®, Orion Laboratories Pty Ltd.

1 Purpose of submission

1.1 The submission requested a General Schedule, Authority Required (STREAMLINED) listing of progesterone (Oripro®) 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-utility analysis (Table 1).

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

Component	Description
Population	Women with singleton pregnancies at risk due to shortened cervix (mid-trimester sonographic cervix ≤25 mm) and/or where there is a history of spontaneous preterm birth.
Intervention	Progesterone (Oripro) 200 mg daily (at night), initiated during the second trimester (16-24 weeks gestation) and continued to the end of the 36th week of gestation or delivery.
Comparator	BSC
Outcomes	Risk of preterm birth (<34 weeks gestation), neonatal mortality.
Clinical claim	In women with singleton pregnancies at risk due to shortened cervix (mid-trimester sonographic cervix ≤25 mm) and/or where there is a history of spontaneous preterm birth, Oripro is more effective than BSC at improving/reducing the risk of preterm birth (<34 weeks gestation) and reduces neonatal deaths.

Source: Table 1, p2 of the submission.
BSC = best supportive care

2 Background

Registration status

2.1 Oripro received TGA approval for use in women at risk of preterm birth in singleton pregnancies on 12 November 2019. The TGA approved indication is: "For the prevention of preterm birth in singleton pregnancies at risk due to shortened cervix (midtrimester sonographic cervix ≤25 mm) and/or where there is a history of spontaneous preterm birth."

3 Requested listing

3.1 The requested listing proposed in the submission is summarised below with suggested additions in italics and deletions in strikethrough.

MEDICINAL PRODCUT, medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
PROGESTERONE 200 mg pessary, 15 doses	NEW	2	30	5	Oripro®

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

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction Type – ☒ Authority Required – Streamlined [new code]
	Condition: Prevention of preterm birth
	Indication: Prevention of preterm birth
	Treatment Phase: ~~Initial and continuing~~
	Clinical criteria:
	Patient must have a singleton pregnancy
	AND
	Clinical criteria:
	~~Patient must be at risk of preterm birth in singleton pregnancies due to:~~ Patient must have a ~~Shortened~~ *short* cervix (mid-trimester sonographic cervix ≤25 mm); or
	~~Where there is~~ *Patient must have* a history of spontaneous preterm birth.
	~~**Administrative advice:** ***Prescriber instructions:***~~ ~~The treatment must be administered for the prevention of preterm birth at a dosage of 200 mg daily (at night). Treatment can be initiated during the second trimester (16-24 weeks gestation) and is to be continued to the end of the 36th week of gestation or until delivery.~~
	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 maximum quantity of 2 packs would allow for 30 days of therapy (2 × 15 pessaries), and 5 repeats would allow for 6 months of therapy. Treatment can be initiated at 16 weeks and go through to 36 weeks or delivery. Each script provides one month of treatment; however, there is potential for wastage when usage would be less than a month, which would be dictated by when treatment commences and the date of delivery.

3.3 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 identified the target population as women with a shortened cervix (mid-trimester sonographic cervix ≤25 mm) and/or with a history of spontaneous preterm birth. The submission noted that it has been estimated that preterm births affect 11% of all pregnancies globally, and based on current Australian Institute of Health and Welfare (AIHW) figures, approximately 8.7% of infants are born before 37 weeks gestation every year. The ESC acknowledged the risk factors of previous spontaneous pre-term birth and a shortened cervix on ultrasound, in line with the proposed PBS population, and also identified additional risk factors of smoking,

Aboriginal/Torres Strait Islander descent and lack of support/socio-economic disadvantage.

4.2 The submission stated that based on 2018 AIHW data, 79.9% of preterm births are admitted to special care nursery/neonatal intensive care units (SCN/NICU). The most significant cause of early neonatal mortality and morbidity is respiratory distress syndrome. For preterm infants that survive the neonatal period, there is an increased risk of death during childhood due to increased risks of infection and other illnesses. The submission cited a publication by Cheong (2017) suggesting that moderate-to-late preterm infants (32 to 36 weeks) have worse cognitive, language and motor development when assessed at 2 years of age, and odds of developmental delay were higher for these infants.

4.3 The submission noted there is also risk for the mothers, as a systematic review and meta-analysis (Wu 2018) showed that preterm birth was associated with an increased risk of maternal future cardiovascular disease, death and stroke. Another systematic review (Neiger 2017) showed that women who delivered prematurely had an increase in other morbidities such as metabolic syndrome, blood pressure, central adiposity and kidney disease.

4.4 Oripro is a pessary form of progesterone (200 mg). Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta and adrenal gland. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.

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

5 Comparator

5.1 The submission nominated best supportive care (BSC) as the main comparator. This was appropriate, although the submission did not provide any description of what constituted BSC. The economic model included obstetric visits and ultrasound costs for BSC, the latter for diagnosis of shortened cervix. To maintain consistency with other submissions, BSC has been changed to standard of care (SOC).

5.2 The submission stated (p7) that there are no other pharmacologic treatments prescribed to reduce the risk of preterm birth. The submission also noted that another treatment for preterm birth prevention is cervical cerclage, which is a surgical procedure. The submission indicated cervical cerclage is used in higher risk women who experience progressive cervical shortening with or without progesterone use, and therefore would be used in addition to progesterone. Current guidelines suggest that cervical cerclage can be used where there is both a history of preterm birth and a shortened 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 did not include discussion of Utrogestan® (progesterone) as a near market comparator. Utrogestan was also considered at the November 2020 PBAC Meeting for the same PBS population.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (HCPs) (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from one HCP described the evidence in support of using vaginal progesterone for women at risk of preterm birth due to early cervical shortening to be overwhelming and strongly supported progesterone being listed on the PBS for this purpose. The HCP further commented that for many women who cannot access progesterone through hospital pharmacies, the costs may be prohibitive especially for socially disadvantaged women who are often at higher risk of preterm birth.

6.3 The Preterm Infants Parents Association Inc. (PIPA) provided information regarding the emotional and financial stress for parents of infants born preterm, in relation to survival of the baby, and also long term outcomes such as cerebral palsy, visual or hearing impairment, neurological impairment (autism, intellectual delays and impairment) and many other hurdles. They stated it is also a huge cost to the community as a whole: the cost of looking after preterm babies in neonatal nurseries as well as the cost of care for those children/adults who continue to experience challenges throughout their lives place a large burden on the health budget. They stated that progesterone is used in the Australian Preterm Birth Alliance's program, The Full Nine Months, with considerable success.

6.4 The Australian Preterm Birth Prevention Alliance commented that use of vaginal progesterone is a cornerstone of their strategy to lower the rate of preterm birth in Australia. They first launched their program in Western Australia in mid-2014 with seven strategies, with the principal intervention being the use of vaginal progesterone for a shortened cervix found at midpregnancy ultrasound imaging and for a past history of spontaneous preterm birth, accompanied by introduction of cervix length measurement at all 19 week morphology scans. They stated that in the first full calendar year (2015) the rate of preterm birth state-wide fell by 7.6% and by 20% in the single tertiary perinatal centre.

6.5 The Australian Preterm Birth Prevention Alliance further commented that while the rate of preterm birth in Australia is 8–9%, it is almost double at 15% in Indigenous Australians. They stated that the Kimberley region has a high indigenous population and many of these women are referred to Perth during late pregnancy to prevent or manage preterm labour. Following a decision to make progesterone free in the

Kimberley region, the Alliance claimed that the rate of preterm birth was dramatically reduced in women who had been identified to be at high risk following a mid-pregnancy scan. The Alliance stated that the Kimberley region was the only area in rural Western Australia to effectively lower the rate of preterm birth between 2016 and 2017, following the implementation of free progesterone treatment[1].

6.6 The Australian Preterm Birth Prevention Alliance argued that prevention of preterm birth should be one of the highest priorities in the health care system, and that safely lowering the rate of preterm birth will save lives and prevent disability.

Clinical trials

6.7 The submission presented 11 trials; meta-analyses of those trials formed the basis of the clinical claim. Details of the trials presented in the submission are provided in Table 2.

[1] 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.

Table 2: Trials and associated reports presented in the submission

Trial ID	Publication title	Publication citation
Akbari 2009	Akbari S, Birjandi M, Mohtasham N. Evaluation of the effect of progesterone on prevention of preterm delivery and its complications.	*Sci J Kurdistan Univ Medical Sci.* 2009; 14(3): 11-19.
Arya 2018	Arya R. Randomized trial of natural micronized progesterone in prevention of preterm birth in women at high risk.	*BJOG* 2018; RCOG World Congress 125(S1): 67 *(abstract)*.
Azargoon 2016	Azargoon A, Ghorbani R, Aslebahar F. Vaginal progesterone on the prevention of preterm birth and neonatal complications in high risk women: a randomized placebo-controlled double-blind study.	*Int J Reprod Biomed (Yazd)* 2016: 14(5): 309-316.
Crowther 2017	Crowther, CA, Ashwood P, McPhee AJ, Flenady V et al. Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS Study): A multicentre, randomised, placebo-controlled trial.	*PLoS Medicine* 2017; 14(9): e1002390.
da Fonseca 2003	da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study.	*Am J Obstet Gynecol* 2003; 188: 419-424.
Fonseca 2007	Fonseca EB, Celik E, Parra M et al. Progesterone and the risk of preterm birth among women with a short cervix.	*NEJM* 2007; 357: 462-469.
Hassan 2011	Hassan SS, Romero R, Vidyadhari D et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicentre, randomized, double-blind, placebo-controlled trial.	*Ultrasound Obstet Gynecol* 2011; 38: 18-31.
Majhi 2009	Majhi P, Bagga R, Kalra J, Sharma M. Intravaginal use of natural micronized progesterone to prevent pre-term birth: a randomised trial in India.	*J Obstet Gynaecol* 2009; 29(6): 493-498.
Norman 2016	Norman JE, Marlow N, Messow CM, Shennan A et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial.	*Lancet* 2016; 387(10033): 2106-2116.
O'Brien 2007	O'Brien JM, Adair CD, Lewis DF et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. DeFranco EA, O'Brien JM, Adair CD, Lewis DF et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial.	*Ultrasound Obstet Gynecol* 2007; 30(5): 687-696. *Ultrasound Obstet Gynecol* 2007; 30(5): 697-705.
Triple P trial	van Os MA, van der Ven AJ, Kleinrouweler CE, Schuit E et al. Preventing preterm birth with progesterone in women with a short cervical length from a low-risk population: A multicenter double-blind placebo-controlled randomized trial. Van't Hooft J, Cuijpers C, Schneeberger C, Van Der Lee JH et al. Preventing preterm birth with progesterone in women with short cervical length, outcomes in children at 24 months of age.	*Am J Perinatol* 2015; 32(10): 993-1000. *Am J Obstet Gynecol* 2017; 216: S492 *(abstract)*.

Source: Table 6, p21-24 of the submission.

6.8 While the literature searches were satisfactory in that relevant trials were identified, the searches did not identify additional publications that were potentially also relevant, such as a Cochrane overview of systematic reviews of interventions to

prevent preterm birth (Medley 2018[2]), as well as additional reviews and discussion of the use of progesterone in pregnancy (e.g. Prior 2017[3]). The ESC considered that these reviews supported the clinical claim for progesterone for the requested PBS population. The ESC noted that the Patient-Centred Outcomes Research Institute (PCORI) is undertaking a large, individual level meta-analysis[4], which should provide more definitive evidence for the effectiveness of progesterone in preterm birth.

6.9 The key features of the selected trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ location	Risk of bias	Study population	Outcome(s)	Use in economic model
Akbari 2009	Progesterone 100 mg: N=75 SOC: N=75 Total: N=150	R Iran Abstract only	High	Asymptomatic with high risk singleton pregnancies	Preterm delivery <34 weeks; <37 weeks; gestational age at delivery	Meta-analysis of Akbari 2009, Azargoon 2016, Crowther 2017, Fonseca 2007, Hassan 2011, Norman 2016, O'Brien 2007 and Triple P trial for neonatal death. Meta-analysis of Akbari 2009, Azargoon 2016, da Fonseca 2003, Fonseca 2007, Majhi 2009, Norman 2016 and Triple P trial for preterm birth.
Arya 2018	Progesterone 100 mg: N=41 SOC: N=40 Total: N=81	R India Abstract only	High	High risk for preterm delivery	Preterm delivery	
Azargoon 2016	Progesterone 400 mg: N=50 SOC: N=50 Total: N=100	R, DB Iran	Low	History of preterm birth; history of preterm birth and short cervix (≤28 mm)	Preterm delivery <34 weeks; <37 weeks; gestational age at delivery; infant mortality	
Crowther 2017	Progesterone 100 mg: N=398 SOC: N=389 Total: N=787	R, DB, MC Australia, New Zealand, Canada	Low	History of spontaneous preterm birth	Respiratory distress syndrome	
da Fonseca 2003	Progesterone 100 mg: N=72 SOC: N=70 Total: N=142	R, DB Brazil	Low	Asymptomatic high risk singleton pregnancies	Preterm delivery <37 weeks; <34 weeks	
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	
Hassan 2011	Progesterone gel 90 mg: N=236 SOC: N=229 Total: N=465	R, DB, MC USA, India, Ukraine, Belarus, Italy, Czech Republic, Russia, South Africa, Chile	Low	Singleton pregnancy, cervical length 10-20 mm	Preterm delivery <33 weeks	
Majhi 2009	Progesterone 100 mg: N=50 SOC: N=50 Total: N=100	R India	High	≥1 prior spontaneous preterm birth	Preterm delivery <37 weeks; <34 weeks	

[2] 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.

[3] 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.

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

Trial	N	Design/ location	Risk of bias	Study population	Outcome(s)	Use in economic model
Norman 2016	Progesterone 200 mg: N=618 SOC: N=610 Total: N=1228	R, DB, MC UK, Sweden	Low	Previous spontaneous birth ≤34 weeks or cervical length ≤25 mm	Fetal death or birth <34 weeks; composite of death, brain injury or bronchopulmonary dysplasia; standardised cognitive score at 2 years of age	
O'Brien 2007	Progesterone gel 90 mg: N=332 SOC: N=327 Total: N=689	R, DB, MC USA, India, Czech Republic, Chile, South Africa	Low	History of spontaneous preterm birth	Preterm delivery <32 weeks	
Triple P trial 2015	Progesterone 200 mg: N=41 SOC: N=39 Total: N=80	R, DB, MC Netherlands	Low	Singleton pregnancy without history of preterm birth and cervical length ≤30 mm	Composite adverse neonatal outcome[a]	

Source: Table 11, p38-40 of the submission.

DB=double blind; MC=multi-centre; R=randomised; SOC=standard of care

[a] Composite outcome comprised of respiratory distress syndrome, bronchopulmonary dysplasia, intracerebral haemorrhage > grade II, necrotizing enterocolitis > stage 1, proven sepsis or death before discharge

6.10 The submission included two abstracts (Akbari 2009; Arya 2018); the limited available information made it difficult to appropriately assess risk of bias in those studies.

6.11 Of the included trials, three (Fonseca 2007; Norman 2016; Triple P trial 2015) used the progesterone dose sought in the requested listing (200 mg). The Fonseca (2007) trial included women with cervical length ≤15 mm, which differed from the ≤25 mm in the requested PBS population. The Triple P trial (2015) required that women did not have a history of preterm birth, and that women had cervical length ≤30 mm. While the requested restriction specifying cervical length of ≤25 mm would be included in a population with cervical length ≤30 mm, the outcomes would only apply to a subgroup of the requested PBS population since the trial excluded women with a history of preterm birth.

6.12 The Norman 2016 trial included women with a history of preterm birth or a shortened cervix (≤25 mm) and therefore corresponded to the population in the requested listing. Hence, the Norman 2016 trial was the only trial presented that used the requested dose of progesterone (200 mg) and had a study population that included the proposed PBS population of both previous spontaneous birth ≤34 weeks and cervical length ≤25 mm. While this trial showed no statistically significant advantages for progesterone, the ESC noted that only a subset of the population reported in the

Norman 2016 study met the proposed PBS criteria.[5] Also, the pre-sub-committee response (PSCR) stated that the outcomes of this study may have been affected by the shortened duration of treatment, as treatment started between 22 and 24 weeks and continued to 34 weeks gestation, whereas the Product Information for Oripro recommends that treatment is initiated during the second trimester (16–24 weeks gestation) and is continued to the end of the 36th week of gestation or until delivery.

6.13 The submission noted that Romero 2016 reported no difference in effect for 90 mg – 100 mg and 200 mg progesterone. The Romero 2016 meta-analysis included Fonseca 2007, O'Brien 2007, Hassan 2011, Norman 2016 and Cetingoz 2011, and reported that the interaction effect of vaginal progesterone based on daily dose was non-significant (p=0.65).

6.14 The submission did not identify an overview of Cochrane systematic reviews (Medley 2018, paragraph 6.8), 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 such options as 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.

6.15 A systematic review and meta-analysis by Prior 2017, also not identified in the submission (paragraph 6.8), discussed that earlier studies and reviews may have been biased by either selective publication or selective choice of outcomes. 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 World Health Organization [6]) 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 I^2 value of 33%, indicating some heterogeneity. The PSCR stated that Prior 2017 was not relevant to the proposed intervention and PBS population: three trials (Martinez, Palacio, Sharami) were conducted in women whose preterm labour had already commenced, as opposed to prevention of preterm birth through pre-emptive treatment; and two studies (Grobman, Tan) used the wrong intervention (17 alpha-hydroxyprogesterone caproate). The three relevant studies (Hassan 2011, Norman 2016, O'Brien 2007) were included in the submission analysis.

6.16 A systematic review by Jarde 2019[7] was excluded by the submission because six of the studies used the wrong intervention (17 alpha-hydroxyprogesterone caproate;

[5] 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].

[6] WHO International Clinical Trials Registry Platform is available at: https://www.who.int/ictrp/network/primary/en/

[7] Jarde A, Lutsiv O, Beyene J, McDonald SD. Vaginal progesterone, oral progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis. *BJOG* 2019; 126: 556-567.

Grobman, Ibrahim, Johnson, Meis, Saghafi, Shahgheibi); two used the wrong administration route (oral progesterone; Glover, Rai); and one study included the wrong population (Cetingoz) (PSCR). However, the ESC noted that the overall conclusion of the review was 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".

Comparative effectiveness

6.17 Table 4 provides the key results from the submission's meta-analyses.

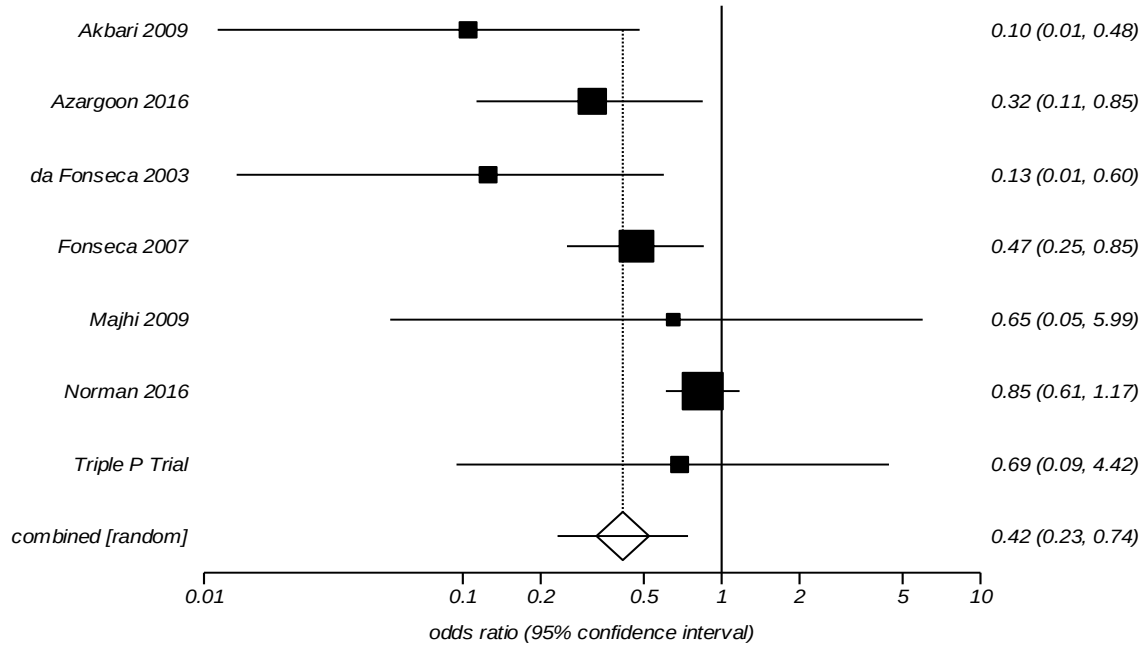
Table 4: Individual trial and meta-analysis results for neonatal death, preterm birth and respiratory distress syndrome

Outcome/trial	Progesterone n/N (%)	SOC n/N (%)	OR (95% CI)	RR (95% CI)	I^2
Neonatal death					
Azargoon 2016	2/51 (4)	21/52 (42)	**0.06 (0.01, 0.28)**	**0.10 (0.03, 0.34)**	
Crowther 2017	1/406 (0.2)	2/393 (0.5)	0.48 (0.01, 9.32)	0.48 (0.06, 3.68)	
Fonseca 2007	2/125 (1.5)	7/125 (5.1)	0.27 (0.03, 1.49)	0.29 (0.07, 1.18)	
Hassan 2011	3/235 (1.3)	5/223 (2.2)	0.56 (0.09, 2.94)	0.54 (0.15, 2.13)	
Norman 2016	1/600 (<1)	6/597 (1)	0.16 (0.00, 1.36)	0.17 (0.03, 1.04)	
O'Brien 2007	6/309 (1.9)	7/302 (2.3)	0.83 (0.23, 2.94)	0.84 (0.30, 2.35)	
Triple P Trial	1/41 (2.4)	2/39 (5.1)	0.46 (0.01, 9.32)	0.48 (0.06, 3.51)	
Meta-analysis (fixed effect)	19/1842 (1.0%)	60/1806 (3.3%)	**0.29 (0.17, 0.50)**	**0.31 (0.19, 0.52)**	22.3%
Preterm birth <28 weeks					
Hassan 2011	12/235 (5.1%)	23/223 (10.3%)	0.47 (0.21, 1.01)	**0.50 (0.25, 0.96)**	
O'Brien 2007	10/309 (3.2%)	9/302 (3.0%)	1.09 (0.39, 3.08)	1.09 (0.46, 2.57)	
Meta-analysis	22/544 (4%)	32/525 (6.1%)	0.64 (0.37, 1.12)	0.66 (0.39, 1.12)	NR
Preterm birth <34 weeks					
Akbari 2009	2/69 (2.9%)	16/72 (22.2%)	**0.10 (0.01, 0.48)**	**0.13 (0.03, 0.48)**	
Azargoon 2016	9/51 (18%)	21/52 (42%)	**0.32 (0.11, 0.85)**	**0.44 (0.22, 0.84)**	
da Fonseca 2003	2/72 (2.8%)	13/70 (18.6%)	**0.13 (0.01, 0.60)**	**0.15 (0.04, 0.56)**	
Fonseca 2007	26/125 (20.8%)	45/125 (36.0%)	0.47 (0.25, 0.85)	**0.58 (0.38, 0.87)**	
Majhi 2009	2/50 (4%)	3/50 (6%)	0.65 (0.05, 5.99)	0.67 (0.14, 3.21)	
Norman 2016	88/592 (15%)	101/590 (17%)	0.85 (0.61, 1.17)	0.87 (0.67, 1.13)	
Triple P Trial	3/41 (7.0%)	4/39 (10%)	0.69 (0.09, 4.42)	0.71 (0.19, 2.69)	
Meta-analysis (random effects)	132/1000 (13.2%)	203/998 (20.3%)	**0.42 (0.23, 0.74)**	**0.51 (0.32, 0.80)**	63.9%
Respiratory distress syndrome					
Akbari 2009	5/69 (7.2%)	23/72 (31.9%)	**0.17 (0.05, 0.50)**	**0.23 (0.09, 0.54)**	
Azargoon 2016	10/51 (20%)	21/52 (42%)	**0.36 (0.13, 0.94)**	**0.49 (0.25, 0.90)**	
Crowther 2017	42/402 (10.5%)	41/388 (10.6%)	0.99 (0.61, 1.60)	0.99 (0.66, 1.48)	
Fonseca 2007	11/125 (8.1%)	19/125 (13.8%)	0.54 (0.22, 1.26)	0.58 (0.29, 1.15)	
Hassan 2011	7/235 (3.0%)	17/223 (7.6%)	**0.37 (0.13, 0.97)**	**0.39 (0.17, 0. 90)**	
O'Brien 2007	34/309 (11.0%)	36/302 (11.9%)	0.91 (0.54, 1.55)	0.92 (0.60, 1.43)	
Triple P Trial	2/41 (5%)	2/39 (6%)	0.95 (0.07, 13.73)	0.95 (0.17, 5.21)	
Meta-analysis (random effects)	111/1232 (9%)	159/1201 (13.2%)	**0.55 (0.34, 0.88)**	**0.61 (0.41, 0.90)**	60.6%

Source: Table 19, p67-68; Table 20, p68; Table 26, p72 of the submission.
CI=confidence interval; NA=not applicable; NR=not reported; OR=odds ratio; RR=relative risk; SOC=standard of care; bold=statistically significant

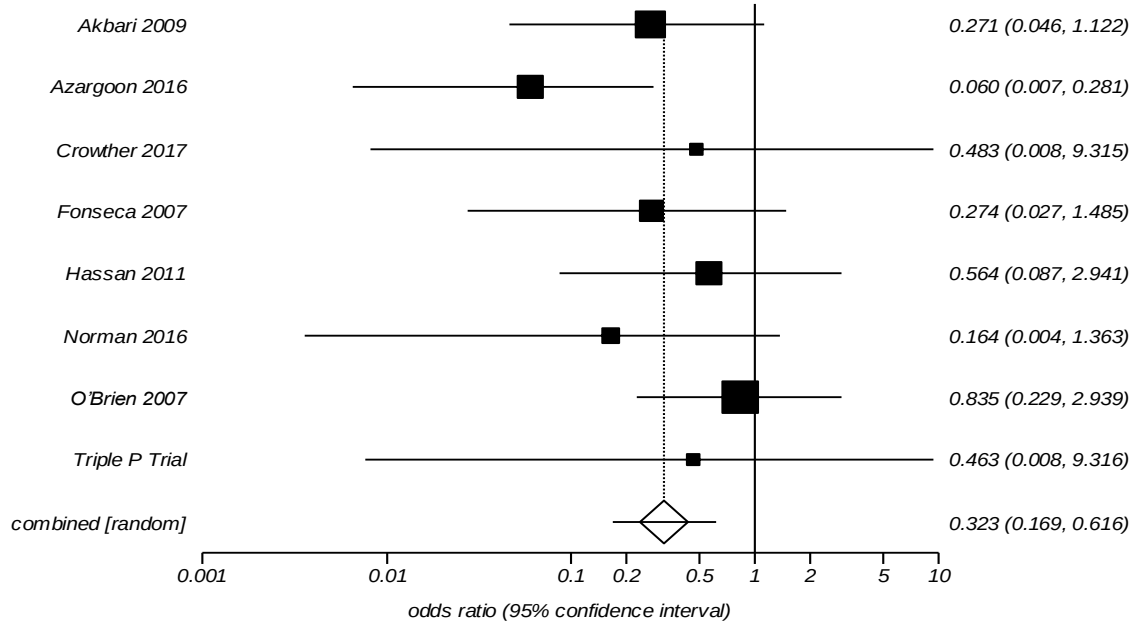
6.18 The PSCR provided Forest plots using a random effects odds ratio analysis for preterm birth at <34 weeks and neonatal mortality. The Forest plots are shown in Figure 1 and Figure 2, respectively.

Figure 1: Random effects odds ratio meta-analysis of preterm birth (<34 weeks)



Source: Section 1.3.1 of the Statistical Analyses Attachment to the submission (Oripro_PBACJuly2020_StatisticalAnalysis.docx)

Figure 2: Random effects odds ratio meta-analysis of neonatal mortality



Source: Section 1.6.1 of the Statistical Analyses Attachment to the submission (Oripro_PBACJuly2020_StatisticalAnalysis.docx)

6.19 The results show statistically significant advantages for progesterone for neonatal death, preterm birth at <34 weeks and respiratory distress syndrome. The PSCR stated (p2) that although the trials included in the meta-analysis were small investigator-driven studies, the studies consistently favoured progesterone and demonstrated that women who received vaginal progesterone experienced a clinically important 49% decrease in the risk of preterm birth at <34 weeks' gestation (Figure 1, Table 4). The PSCR also stated that vaginal progesterone significantly reduced the risk of neonatal mortality by 69% (1.0% vs 3.3%) compared with placebo/no treatment (Figure 2, Table 4).

6.20 The ESC noted that while the confidence intervals for many of the individual trials exceeded 1, all point estimates for neonatal death, preterm birth <34 weeks and respiratory distress syndrome favour the use of progesterone. The ESC also noted that the meta-analysis conducted by the sponsor for preterm birth <34 weeks (relative risk (RR) = 0.51 [95% CI 0.32, 0.80]) was consistent with that presented by the Romero 2018 meta-analysis (RR for preterm birth <34 weeks = 0.63 [95% CI 0.44, 0.88]).

6.21 The ESC observed that in a comparison of meta-analysis results between the sponsor's submission, NICE 2019 and Romero 2018, the results presented in the submission are consistently more optimistic than presented by NICE 2019 or Romero 2018. The number needed to treat (NNT) to avoid one preterm birth is 7 using the sponsor's analysis, compared with 12 using Romero 2018 results.

6.22 All analyses conducted by the Sponsor, with the exception of neonatal death, showed a substantial amount of inconsistency, with I^2 values above 60%. This would indicate results should be interpreted with caution. The PSCR noted that for the outcome of neonatal death, the results demonstrated limited inconsistency with an I^2 of only 22.3%. A benefit was not demonstrated for progesterone for preterm birth at <28 weeks (nor <32 weeks).

6.23 The meta-analysis outcomes of preterm birth at <34 weeks and neonatal death were used in the economic model. The submission also assessed longer-term neurodevelopmental outcomes. The results for the Bayley-III cognitive composite score and neurodevelopmental impairment are provided in Table 5. These analyses showed no statistically significant difference between progesterone and SOC.

Table 5: Individual trial and meta-analysis results for neurodevelopmental outcomes

Trial ID	N	Progesterone Mean ± SD	N	SOC Mean ± SD	Mean difference (95% CI)	
Bayley-III cognitive composite score (2 years follow-up)						
Norman 2016	618	97·3 ± 17·9	610	97·7 ± 17·5	–0.02 (–0.13, 0.09)	
Triple P Trial	28	101.6 ± 9.7	29	105.0 ± 12.5	–0.30 (–0.82, 0.22)	
Meta-analysis	646	97.5 ± 17.6	639	98 ± 17.3	–0.71 (–2.59, 1.16)	
Neurodevelopmental impairment (2 years follow-up)						
		Progesterone n/N (%)		**SOC n/N (%)**	**OR (95% CI)**	**RR (95% CI)**
Norman 2016		47/379 (12%)		35/403 (9%)	1.49 (0.92, 2.44)	1.43 (0.95, 2.16)
Triple P Trial		2/27 (7%)		1/27 (4%)	2.08 (0.10, 127.35)	2 (0.28, 14.81)
Meta-analysis		49/406 (12.1%)		36/430 (8.4%)	1.51 (0.96, 2.37)	1.44 (0.96, 2.17)

Source: Table 27, p72; Table 28; p73 of the submission.
CI=confidence interval; OR=odds ratio; RR=relative risk; SOC=standard of care

6.24 The results for neurodevelopmental impairment for the Triple P trial had very wide confidence intervals (e.g. 0.10 to 127.35) and the N and results reported by the submission did not correspond to the source publication.

Comparative harms

6.25 The submission stated (p75) there was limited data on the incidence of adverse events (AEs) reported in the publications, and the rate of AEs was not significantly different for women who received progesterone and those who received SOC. The submission provided occurrence of AEs from three of the selected trials, the overall number of women reporting AEs in the Romero (2018) meta-analysis, as well as between-group statistical comparisons for the identified AEs. Those results are provided in Table 6.

Table 6: Summary of key adverse events in the trials

Trial/AEs	Progesterone n/N (%)	SOC n/N (%)	Adjusted treatment effect (95% CI)
Crowther 2017			
Reported AEs	134/394 (34.0%)	118/382 (30.9%)	1.11 (0.90, 1.36)
Headache	39/394 (9.9%)	35/382 (9.2%)	1.07 (0.69, 1.65)
Nausea	33/394 (8.4%)	24/382 (6.3%)	1.33 (0.80, 2.21)
Pain or discomfort	29/394 (7.4%)	29/382 (7.6%)	0.96 (0.59, 1.56)
Breast tenderness	12/394 (3.1%)	16/382 (4.2%)	0.72 (0.34, 1.49)
Coughing	10/394 (2.5%)	5/382 (1.3%)	NA
Other	66/394 (16.8%)	58/382 (15.2%)	1.13 (0.82, 1.55)
Triple P trial 2015			**RR (95% CI)**
Reported AEs	4/41[a] (12%)	7/39(24%)	0.51 (0.16, 1.61)
Pain or discomfort	1/41 (3%)	0/39(0%)	NR
Vaginal discharge	4/41 (12%)	5 (17%)	0.77 (0.22, 2.7)
Itching	2/41 (6%)	3/39 (10%)	0.59 (0.11, 3.29)
Local irritation	1/41(3%)	0/39 (0%)	NA
Redness	0/41 (0%)	0/39 (0%)	NA
O'Brien 2007			
Vaginal discharge	8.4%	9.2%	NR
Romero 2018			
Reported AEs	51/424 (12%)	47/422 (11%)	OR=1.10 (0.87, 1.40)[b] RR=1.21 (0.87, 1.69)[b]

Source: Table 32 p75-76 of the submission.

AEs=adverse events; CI=confidence interval; NA=not available; NR=not reported; OR=odds ratio; RR=relative risk; SOC=standard of care

[a] The submission reported the Triple P trial (2015) as having an N of 27, however that value was not reported anywhere in the publication as an N. Instead, the progesterone group had an N of 41, which has been reported here.

[b] The submission reported an OR value for Romero (2018) however the publication reported a RR value. Both are provided here.

6.26 There were no statistically significant differences in the occurrence of AEs between women treated with progesterone and those treated with SOC in the three trials (Crowther 2017; Triple P trial 2015; O'Brien 2007). There were only a small number of different event types reported, but occurrence was similar across both treatment arms.

Benefits/harms

6.27 A summary of the comparative benefits and harms for progesterone versus SOC is presented in Table 7.

Table 7: Summary of comparative benefits and harms for progesterone and SOC

Analysis	Progesterone n/N (%)	SOC n/N (%)	OR (95% CI)	Event rate/100 women*		RR (95% CI)
				Progesterone	SOC	
Benefits						
Neonatal death						
Submission meta-analysis	19/1842 (1.0%)	60/1806 (3.3%)	**0.29 (0.17, 0.50)**	1.0	3.3	**0.31 (0.19, 0.52)**
Preterm birth <34 weeks						
Submission meta-analysis	132/1000 (13.2%)	203/998 (20.3%)	**0.42 (0.23, 0.74)**	13.2	20.3	**0.51 (0.32, 0.80)**
Harms						
No significant differences						

Source: Table 33, p77 of the submission

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

* Treatment duration ranged from 10 to 20 weeks in the meta-analyses.

6.28 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 20 weeks:

- Approximately 2 fewer neonatal deaths would occur.
- Approximately 7 fewer mothers would have preterm birth of newborns at <34 weeks.
- There would be no difference in adverse events between those treated with progesterone and those treated with SOC.

6.29 The ESC noted that the reduction in the number of preterm births was significant with no difference in harms.

Clinical claim

6.30 The submission described vaginal progesterone (Oripro) as superior to SOC in terms of effectiveness and non-inferior in terms of safety.

6.31 The PBAC noted that the clinical evidence was of variable quality and applicability to the proposed PBS population. Also, many of the meta-analysis results presented by the submission had substantial variation, signified by I^2 values of 60% or greater. While the submission claimed that the meta-analysis results were consistent with published results, i.e. Romero (2018), the more favourable analyses conducted by the submission were applied in the economic model (paragraph 6.20). Furthermore, many of the individual trials included in the meta-analyses showed no benefit for progesterone. The sponsor reasoned that although the trials included in the meta-analysis were small investigator-driven studies, the studies consistently favoured progesterone and demonstrated that women who received vaginal progesterone experienced a clinically important decrease in the risk of preterm births at <34 weeks' gestation and significantly reduced the risk of neonatal mortality compared with SOC.

6.32 The sponsor stated in the PSCR that the consensus of The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) is as follows:

- Vaginal progesterone therapy is recommended for asymptomatic women with a short cervix (<25 mm) on transvaginal cervical length assessment in the midtrimester;
- Progesterone therapy should be considered for women with a singleton pregnancy with a history of previous spontaneous preterm singleton birth.

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

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

6.35 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.

Economic analysis

6.36 The submission presented a stepped economic evaluation including a cost-utility analysis (Table 8).

Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Progesterone (Oripro) versus SOC.
Time horizon	20 years in the model base case versus 10-19 weeks in the trials.
Outcomes	Risk of preterm birth (<34 weeks gestation), neonatal mortality, QALYs.
Methods used to generate results	Decision tree model.
Cycle length	Monthly for 5 months then yearly up to 20 years.
Transition probabilities	Meta-analysis of clinical trials.
Extrapolation method	Australian life tables.
Health related quality of life	Literature-based (Clemens 2014).

Source: Table 40, p90 of the submission.

6.37 The economic model had two phases. The first 5 month phase covered the administration of progesterone and birth of a child, while the second phase encompassed the first 20 years of the newborn's life. While this model structure has potential advantages, including assessing impact of progesterone on preterm birth and also assessing impact on the newborn, there is inherent uncertainty regarding the cost-effectiveness of Oripro, given that very little is known about the longer term consequences of progesterone on pre-term children. Further, because the model applied values from the first 5 months to Year 0 in the first 20 years of the newborn's life, the second phase of the model actually covered Year 0 to Year 20, inclusive, which was 21 years. However, the model did not calculate life years and QALYs in the same manner. Life years over the 20 years were the sum of Year 0 to Year 20, while QALYs were based on values in Year 1 to Year 21. The submission provided no explanation as to why these different time periods were used.

6.38 The model used the following costs (Table 9). Notably there was no adjustment for when the pre-term births occur. The ESC considered this reasonable given that there was no evidence of differences at <28 week gestation births. The ESC also noted that longer term morbidity costs attributable to mortality differences were not accounted for.

Table 9: Costs applied in the trial-based analyses and economic model

Component	Cost	Description	Use
Oripro	$[redacted]	Requested price of $[redacted]	Oripro: Cost of 20 weeks of treatment, assuming full compliance. SOC: none
Ultrasound	$101.50	MBS 55706	Oripro: 2 SOC: 1
Obstetric visit	$43.70	MBS 16404	Oripro: 6 (once per month and one extra for ultrasound) SOC: 5 (once per month)
Cost of preterm birth	$11,851.24	AR-DRG 001A, 001B, 001C, 002A, 002B public sector 2016-17 weighted average	Oripro: 1,436[a] SOC: 2,291[a]
Cost of full term birth	$11,851.24		Oripro: 8,534 SOC: 7,328[a]
Cost of preterm baby	$15,548.20	AR-DRG P03A to P68D public sector 2016-17 weighted average	79.9% of preterm babies based on AIHW 2018 Oripro: 1,436[a] SOC: 2,291[a]

Source: Table 54 p108 of the submission.
AIHW=Australian Institute of Health and Welfare; SOC=standard of care
[a] Numbers of births and numbers of preterm babies hospitalised based on the cohort of 10,000 used in the model.

6.39 Following the initial period in the model when newborns could be re-hospitalised, the only activity in the model was life-table based survival. All newborns were assigned the same utility value (0.91) and importantly, the model did not take into consideration key outcomes of preterm birth, including cognitive, language and motor development and associated impact on quality of life. Assessment of these types of outcomes would have allowed for a full consideration of the cost-effectiveness of Oripro.

6.40 The utility value applied in the model was sourced from Clemens 2014, which provided a comparison of EQ-5D-3L population norms in Queensland, estimated using utility value sets from Australia, the UK and USA. While the submission provided a list of utility values for the Australian general population from 18-24 years up to 75+ years, the only value applied in the model was that for 18-24 years old, which was a utility value of 0.91.

6.41 The submission did not justify the application of a utility value sourced from the general Australian population aged 18-24 years to infants from birth onward, and the submission did not incorporate this utility outside of life-table based mortality for the newborns. As the same utility value was applied to both preterm and full term infants from birth for 20 years, and the submission did not validate or rationalise the use of adult-sourced utility values in infants from birth, the cost-utility aspect of the model does not appear to be informative. The ESC agreed with the evaluation that the use of the utility value of 0.91 from Clemens 2014 was uninformative and incorrect. The ESC noted that the published value of 0.91 for 18-24 year olds is too high for children born

preterm. According to the Child Health Utility-9D (CHU-9D) from the Young Minds Matter (YMM) survey (unpublished manuscript, Deakin Health Economics, 2020), utility values for general populations of 11-17 year olds range from 0.84 (11y/o) to 0.74 (16 y/o). Also, the utility for the submission cohort is likely to be lower due to issues with preterm babies. The sponsor argued in the PSCR and the pre-PBAC response that the utility value could be as low as 0.5 and still result in a favourable ICER.

6.42 The ESC considered that while the actual utility value itself was unreasonable, it was reasonable to use the same utilities in both progesterone and SOC groups, as there is no evidence from clinical trials for differential longer term outcomes in babies. The ESC noted that the ICER was not overly sensitive to the utility value.

6.43 Table 10 provides a summary of the key drivers of the model. Table 10 shows the results of the stepped economic evaluation.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Structure	The model is simplistic and not consistently structured. Also longer term costs were not accounted for.	Moderate, likely favours progesterone
Utilities	The single utility value was sourced from a paper providing a comparison of EQ-5D-3L population norms in Queensland, estimated using utility value sets from Australia, the UK and USA and is not likely to be applicable to infants, children and young adults.	Moderate, favours progesterone, limits the relevance of the utility values. The ESC considered that it was reasonable to use the same utilities in both progesterone and SOC groups.

Source: Section 3.2.2, p95-96 of the submission.

Table 11: Results of the stepped economic evaluation

Step and component	Oripro	SOC	Increment
Step 1: trial-based with drug and outpatient costs only			
Costs[a]	$ [redacted]	$ [redacted]	$ [redacted]
Responders	0.86	0.77	0.09
Deaths	0.99	0.97	0.02
Incremental cost/premature birth avoided (responders)			$ [redacted] [1]
Incremental cost/death avoided			$ [redacted] [2]
Step 2: Cost-effectiveness – trial period with all costs			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
Responders	0.86	0.77	0.09
Deaths	0.99	0.97	0.02
Incremental cost/premature birth avoided (responders)			$ [redacted] [1]
Incremental cost/death avoided			$ [redacted] [2]
Step 3: Modelled evaluation – 20 year time horizon (undiscounted)			
Costs	[redacted]	[redacted]	[redacted]
LY	20.61	20.22	0.39
Incremental cost/extra LY gained			$ [redacted] [3]
Step 4: Modelled evaluation – 20 year time horizon (discounted)			
Costs	[redacted]	[redacted]	[redacted]
LY	13.22	12.97	0.25
Incremental cost/extra LY gained (base case)			$ [redacted] [3]
QALY	11.45	11.23	0.22
Incremental cost/extra QALY gained (base case)			$ [redacted] [3]

Source: Table 56, p110-111 of the submission; Excel workbook 'ORIPRO_Preterm_model_illuminatev14.
LY=life year; QALY=quality adjusted life year; SOC=standard of care

[a] The submission used a cohort of 10,000 women, resulting in costs that were close to $150M and QALYs in the thousands. For ease of presentation, a cohort of one has been used here.

The redacted values correspond to the following ranges:
[1]$5,000 to <$15,000/QALY gained
[2]$55,000 to <$75,000/QALY gained
[3]$0 to <$5,000/QALY gained

6.44 While the model produced a cost per QALY that appeared to be cost-effective ($0 to <$5,000/QALY gained), the model did not provide an assessment of the cost-effectiveness of Oripro, for a number of reasons:

- The submission split the model into two phases, the first addressing preterm birth and the second following the life of the newborn for 20 years (which included hospitalisation for preterm babies), however the submission did not consider any potential impacts of preterm birth on later life, which the submission highlighted as a key consequence of preterm birth (cognitive development, illness). The PSCR stated that the benefits alone of reduced infant mortality, together with the lower costs associated with term birth and the very low costs of treatment, is sufficient to justify PBS listing. The sponsor stated that these additional benefits (i.e. reduction in impacts of preterm birth on later life) were not included in the model because it would add uncertainty without changing the overall findings of the model. The sponsor claimed that this was a conservative approach: since the rate of preterm birth was higher in the SOC arm, the addition of clinical benefits associated with term birth and cost offsets would make progesterone more cost effective. The pre-PBAC response stated that the link between the pre-birth phase

and the following twenty years was via reduced mortality associated with Oripro treatment.

- While the model included hospitalisation costs for preterm babies, there were no hospitalisation costs included for babies born full term. Thus, costs associated with each treatment arm were not accurately reflected. The PSCR stated that when a baby is born at term without a complication for the baby, the admission is only for the mother and there is no subsequent admission for the baby; when the baby is preterm there is an additional admission for the baby. However, the AIHW report from which the submission sourced the rate of hospitalisation of 79.9% for preterm babies also indicates that 13% of full-term birth infants are readmitted to hospital. The ESC noted that a proportion of full term babies are also admitted to hospital.
- The submission's rationalisation for a 20 year time horizon cannot be strongly supported, particularly as the only event that happens over the 20 years is life table-based mortality. As noted above (paragraphs 6.20 and 6.31), given a proportion of these children will have been born preterm, the model does not accurately assess the population in question. The PSCR stated that the 20-year time horizon was very conservative, and that there was no basis to conclude that babies who go to term would not have a normal life expectancy. To substantially reduce the length of the model essentially eliminates most of the life year and QALY gains from treatment. The ESC also noted that the evidence suggested that the health impacts on the babies who are born and survive do not differ between the arms in the trials which report such outcomes.

6.45 The ESC noted that the result from the cost utility analysis was not dominant, because the model did not adjust for the actual cost of preterm delivery, instead it assumed an overall rate of delivery. By not adjusting for the cost of preterm delivery, the cost-offsets largely disappear. The ESC considered that this was an appropriate approach to modelling the costs.

6.46 The ESC commented that the model lacked face validity because, while the model had a 20-year time horizon, it generated greater than 20 years undiscounted life years for Oripro. This occurred because values from the 5 monthly cycles pre-birth were used to provide values used in Year 0 of the model, and since the model used Year 0 to Year 20 to provide total life years, the calculated model duration was actually 21 years and 5 months. There are more life years associated with the model (20.61) than the claimed model duration of 20 years and 5 months (20.42). The model also calculated QALY values using a different time period (Year 1 to Year 21), with no explanation as to why the time period was altered for QALY calculations. Applying the Year 0 to Year 20 time period to QALYs decreased the ICER to $0 to <$5,000/QALY gained from the $0 to <$5,000/QALY gained generated by the submission's base case.

6.47 The ESC considered that, according to the model structure as submitted, all costs should accrue in Year 1 of the model because they occur in the perinatal period. The

ESC noted that while costs for a preterm baby were added in Year 1 of the model, this actually represented the second year, as Year 0 was counted as the first year of the model for totalling life years. This did not accurately reflect what would occur in practice, and did not appear to accurately reflect costs for preterm babies, which could result in an average length of stay of 112 days (e.g. ARDRG P07Z).

6.48 The sponsor noted that Utrogestan was also being considered by the PBAC at the November 2020 meeting and stated that while Utrogestan had a lower price per milligram (based on the current PBS listings for assisted reproductive technology (ART)) it was more expensive than Oripro on a daily cost to patient basis. The sponsor requested a weighted average price for Oripro, using the ART and preterm birth prices, and utilisation across those indications. (pre-PBAC response)

Drug cost/pregnancy

6.49 The cost per pregnancy for Oripro (Table 12) was based on the assumption made by the submission that treatment would continue for 20 weeks, at full compliance. This is not likely to be reflected in clinical practice. The PSCR stated that assuming full compliance was a conservative approach which was biased against progesterone. SOC was not assigned any cost in the model and is not included in the table.

Table 12: Intervention costs per pregnancy for Oripro

	Cost of Oripro (requested DPMQ $[redacted])
Per day	$[redacted]
Per week	$[redacted][a]
Per month	$[redacted][b]
20 weeks (as used in economic model and financial estimates)	$[redacted][c]

Source: Table 52, p105 of the submission.

[a] The cost per week was based on cost per day ($[redacted]) × 7.

[b] The cost per month was based on cost per day ($[redacted]) × 30.

[c] The cost per 20 weeks, or course of treatment was based on cost per month (which is DPMQ) × 5.

Estimated PBS usage & financial implications

6.50 This submission was considered by DUSC.

6.51 The submission applied an epidemiological approach to develop the financial estimates. The submission provided estimates of women with singleton pregnancy and cervix length ≤25 mm and estimates of women with a singleton pregnancy and a history of preterm birth. A summary of the sources used is provided in Table 13.

Table 13: Key inputs for financial estimates

Component	Data source
Epidemiology	
Prevalence data	ABS data: Number of females of child-bearing age (15-44 years): 5.4M in 2021 increasing to 5.8M in 2026. AIHW data: Proportion of pregnant females: 5.83%; singleton births: 295,467 in 2021 increasing to 297,428 in 2026; preterm birth rate in singleton births: 7%. Fonseca 2007: cervical length <25 mm: 10.0%.
Eligible population	52,117 in Year 1 increasing to 54,898 in Year 6.
Utilisation	
Uptake rate	Sponsor assumption: 15% in Year 1, 45% in Year 2, 55% in Year 3, 60% in Year 4, 61% in Year 5, 62% in Year 6.
Treatment duration	Sponsor assumption: 20 weeks.
Compliance	Sponsor assumption: 100%
Number of scripts	36,482 in Year 1, increasing to 158,838 in Year 6.
Cost of medicines	
Oripro	$[redacted] per script; 4.67 packs per pregnancy per course.
Co-payment	Sponsor assumption: 30% of services will be concessional and 70% will be general. Mean co-payment calculated as $30.64 for PBS and $6.60 for RPBS.
Impact on other medicines	
Other agents	Assumed no impact on other medicines.
Agents used to treat AEs	Not included.
MBS usage and costs	
MBS items	Ultrasound (MBS item 55706) and obstetrician visits (MBS item 16404). Usage of these services was based on incremental difference between assumed usage for women treated with Oripro and assumed usage for women treated with SOC. Item cost was applied using an 80% benefit.

Source: Table 4.2, p141; Section 4.1 to Section 4.5, p142-151 of the submission.
AE=adverse event; AIHW=Australian Institute of Health and Welfare; SOC=standard of care

6.52 The sponsor estimated number of pregnancies, script numbers and costs for the PBS listing of Oripro are provided in Table 14.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number initiating treatment	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
Number of scripts dispensed[a]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net financial implications of Oripro						
Net cost to PBS/RPBS	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][5]	$[redacted][6]	$[redacted][6]
Net cost to MBS	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Overall net cost to Government	**$**[redacted][5]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]

Source: Table 65, p122; Table 73 p125 of the submission.
[a] Assuming 4.67 packs per course.
The redacted values correspond to the following ranges:
[1]5,000 to <10,000
[2]20,000 to <30,000
[3]30,000 to <40,000
[4]100,000 to <200,000
[5]$0 to <$10 million
[6]$10 million to <$20 million

6.53 The estimated net cost to Government was $0 to <10M in Year 1, increasing to $10 to <$20M in Year 6, for a total of $90 to <$100M over the first 6 years of listing.

6.54 There is some uncertainty around the proportion of women with cervical length ≤25 mm and/or a history of preterm birth. The proportion of women with a cervix ≤25 mm was estimated from the Fonseca (2007) trial. Based on a sample of close to 25,000 women, 10% had a cervical length ≤25 mm and the submission applied this proportion to its estimates. DUSC considered that there was uncertainty around the proportion of women with cervical length ≤25 mm.

6.55 For the population of women with a shortened cervix, Australian Institute of Health and Welfare (AIHW) data (2018) was used to calculate the proportion of women who were pregnant in the 15–44 age group, which was 5.83%. This rate was applied to the female population for the first 6 years of listing. DUSC noted that based on the AIHW 2018 data, the birth rate had been decreasing. DUSC considered that 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.

6.56 The estimates have not accounted for the potential double-counting of women with a short cervix who also have a history of preterm birth, and the population with a history of prior preterm birth has not been restricted to those women going on to have a subsequent pregnancy, indicating overestimation of treated women. DUSC considered that combining the two populations would result in an overestimate of eligible women from double-counting.

6.57 DUSC considered that as progesterone has a considerable history of use in ART and is familiar to clinicians, the assumed treatment uptake rates in the initial years of listing (15% in Year 1 and 45% in Year 2) were too low. The Sponsor stated in the pre-PBAC response that a large number of clinicians are not experienced with prescribing progesterone for prevention of preterm birth, as it was only recently approved in 2019, and ART is very rarely used in lower socio-economic areas and indigenous communities.

6.58 Based on the recommended dose, the treatment course of Oripro was estimated to be 20 weeks per pregnancy, initiated during the second trimester (16–24 weeks of gestation) and continuing to the 36th week of gestation or delivery. The submission also assumed there would be full compliance to progesterone. DUSC considered that the duration of therapy assumption of 20 weeks was an overestimate. DUSC noted that the median time on progesterone therapy was 14 weeks in the trial evidence presented in the submission. DUSC further considered that the assumption of full compliance was not reasonable, noting that only one of the 11 trials presented in the submission had full compliance.

6.59 DUSC considered that there was a likely pool of women treated with private prescriptions or off-label, which was not factored into the submission's estimates. 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 <=25mm). Based on this definition, DUSC proposed the following method to estimate the eligible population (Table 15).

Table 15: 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 Sponsor stated in the pre-PBAC response that they used an epidemiological approach in the submission to calculate the total number of women eligible for Oripro, including women in private care, who met the criteria for the PBS indication. In light of Utrogestan also being considered by the PBAC at the November 2020 meeting for the same population, the sponsor recalculated the financial estimates of listing Oripro (pre-PBAC response), utilising different uptake rates and the eligible population calculated by DUSC. The duration of treatment was also reduced from 20 weeks to 16 weeks to reflect the minimum dosing in the Product Information. The revised calculations (Table 16) show the net cost of Oripro is $0 to <$10M over the first six years of listing.

Table 16: Revised estimated use and financial implications for progesterone and Oripro

Estimated use and financial implications of progesterone						
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Uptake rate	60%	65%	70%	75%	80%	85%
Number initiating treatment	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to PBS/RPBS	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]
Estimated use and financial implications of Oripro alone						
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Uptake rate[a]	19%	21%	23%	24%	26%	27%
Number initiating treatment	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]
Number of scripts dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Net cost to PBS/RPBS	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]

Source: Table 1, p3 pre-PBAC response.
a Uptake rates for Oripro are 32% of the total uptake of progesterone.
The redacted values correspond to the following ranges:
[1] 10,000 to <20,000
[2] 40,000 to <50,000
[3] 50,000 to <60,000
[4] 500 to <5,000
[5] 5,000 to <10,000s
[6]$0 to <$10 million

6.61 DUSC noted that the financial estimates were based on sensitive assumptions with variations seen in the literature, including the proportion of women with a cervical length ≤25 mm, the time on progesterone therapy and the proportion of singleton births. As such, DUSC considered that a risk-sharing arrangement may be required to manage the uncertainty in the utilisation of progesterone. The Sponsor maintained in the pre-PBAC response that a risk share arrangement (RSA) was not required. 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 was a low barrier to accessing treatment. Therefore the PBAC advised that a RSA would be required.

6.62 DUSC noted there is the potential for off-label use in repeated first term miscarriage. The Sponsor stated in the pre-PBAC response that any such off-label use would be against the TGA-approved indications and RANZCOG guidelines, which state: "The

routine use of progestogens for patients presenting with recurrent spontaneous miscarriage does not improve pregnancy outcomes and is not recommended." The PBAC noted that a Cochrane review[8] suggested progesterone may be beneficial in preventing miscarriage in women with a history of repeated miscarriage. Notwithstanding, 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. Quality Use of Medicines

6.63 The submission provided a description of current quality use of medicines activities, including communication to professionals and education awareness activities. The submission noted that there was a discrepancy in the level of care received by women in metropolitan areas and those in rural and remote communities. The submission stated (p129) this represented a potential opportunity for education and awareness activities to ensure that best practice was implemented across the country, including remote and rural communities. The submission provided no information on how this might be achieved.

6.64 The ESC commented that compliance 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.

6.65 The DUSC commented that in addition to educating women 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.

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of progesterone (Oripro®) for the prevention of preterm birth in women with singleton pregnancies and a short cervix (≤25 mm) and/or a history of preterm birth. The PBAC's recommendation was based on, among other matters, its assessment that the cost-effectiveness of Oripro would be acceptable if it were cost-minimised against Utrogestan®.

7.2 The PBAC was satisfied that Oripro provides, for some women, a significant improvement in efficacy over SOC. The PBAC noted that the submission did not

[8] Haas DM, Hathaway TJ, Ramsey PS. Progestogen 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

provide any description of what constituted SOC, other than including costs for obstetric visits and ultrasounds.

7.3 The PBAC noted that there are no other pharmacologic treatments prescribed to reduce the risk of preterm birth, and that there is a clinical need for prevention of preterm birth in at-risk women. The PBAC noted this was supported by the consumer comments received for this submission.

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 prescription. 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 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.

7.6 The PBAC considered that the restriction should specify:

- It must be a singleton pregnancy
- Patient must have a short cervix (midtrimester cervix ≤25 mm or must have a history of spontaneous preterm birth
- No increase in the maximum quantity or number of units may be authorised.
- No increase in the maximum number of repeats may be authorised.

7.7 The PBAC considered that the sponsor-proposed administrative advice regarding dosage and length of treatment was not required in the restriction.

7.8 The PBAC noted that the clinical evidence was of variable quality and applicability to the proposed PBS population. However, the PBAC accepted that although the trials included in the meta-analysis were small investigator-driven studies, the studies consistently favoured progesterone and demonstrated that women who received vaginal progesterone experienced a clinically important decrease in the risk of preterm births at <34 weeks' gestation and significantly reduced the risk of neonatal mortality compared with SOC. The PBAC considered that while the magnitude of the benefit of progesterone may have been overstated by the Sponsor, it was reasonable to accept that it was associated with a risk reduction in preterm birth.

7.9 The PBAC considered that the economic model lacked validity, as it did not accurately represent when costs associated with preterm babies would occur, and calculated life year gains and QALY gains over different time periods.

7.10 The PBAC considered that the price for Oripro should be no more than for Utrogestan. The equi-effective doses are: one 200 mg Oripro pessary and one 200 mg Utrogestan soft capsule.

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.

7.12 The PBAC considered that an utilisation review by DUSC should be conducted two years after initial listing.

7.13 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.

7.14 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 noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing listing for progesterone as follows:

MEDICINAL PRODUCT, medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
PROGESTERONE progesterone 200 mg pessary, 15	NEW	2	30	5	Oripro

Restriction Summary [new RS1] / Treatment of Concept: [new ToC1]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners ☒Midwives
	Restriction Type – ☒ 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 outcome of the November 2020 PBAC meeting as a major step forward in improving access to a key medicine to help reduce the preterm birth rate in Australia. The Sponsor is disappointed that a Risk Sharing Agreement is being applied considering the low cost of progesterone supplementation for prevention of preterm birth. The percentage of women with a shortened cervix is major factor in

determining size of the eligible population and, whilst there is uncertainty around this, the Sponsor has demonstrated that progesterone not only provides therapeutic benefits but is also the highly cost effective in this population. Therefore the Sponsor believes the risk sharing agreement imposes a significant financial burden and is a threat to the sustainability of an Australian Made product. The sponsor looks forward to working with the Commonwealth further to address this and is committed to ensuring that ORIPRO® is made available for preterm birth prevention.