Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Progesterone

Proprietary Product Name: Oripro

Sponsor: Orion Laboratories Pty Ltd T/A Perrigo Australia

February 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
17-OHPC	17-hydroxyprogesterone caproate
ACM	Advisory Committee on Medicines
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
ASQ	Ages and Stages Questionnaire
CD11b	Cluster of differentiation 11b
CI	Confidence interval
IM	Intramuscular
IPD	Individual patient data
LBS	Literature based submission
MAO	Monoamine oxidase
min	Minute(s)
NICE	National Institute for Health and Care Excellence (UK)
NICU	Neonatal intensive care unit
OR	Odds ratio
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RDS	Respiratory distress syndrome
RI	Resistance index
RMP	Risk management plan
RR	Relative risk

Abbreviation	Meaning
SC	Subcutaneous
SD	Standard deviation
UK	United Kingdom
US	United States

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	6 November 2019
Date of entry onto ARTG:	12 November 2019
ARTG numbers:	21190, 21195, 165111, 165112
, *Black Triangle Scheme*	No
Active ingredient:	Progesterone
Product name:	Oripro
Sponsor's name and address:	Orion Laboratories Pty Ltd T/A Perrigo Australia 25-29 Delawney Street Balcatta WA 6021
Dose form:	Moulded pessary
Strengths:	100 mg, 200 mg
Containers:	Glass jar and strip pack
Pack sizes:	Strip packs: 5 (samples), 15 or 30 Glass jar:15 individually wrapped
Approved therapeutic use:	*Oripro Pessaries are indicated for 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.*
Route of administration:	Vaginal
Dosage:	Adult dosage: prevention of preterm birth The dosage of progesterone for prevention of preterm birth is 200 mg daily (at night). Treatment can be initiated during the second trimester (16 to 24 weeks gestation) and is to be continued to the end of the 36th week of gestation or until delivery. Other intravaginal therapies should not be used while

progesterone pessary treatment is being undertaken.

For further information please refer to the Product Information (PI).

Product background

This AusPAR describes the application by Orion Laboratories Pty Ltd T/A Perrigo Australia (the sponsor) to register Oripro (progesterone) 100 mg and 200 mg vaginal pessary for the following indication:

> *Prevention of preterm birth due to shortened cervix or where there is a history of spontaneous birth between 20 and 34 weeks of gestation (with or without rupture of membranes).*

The most significant and consistently identified risk factors for preterm birth are a short cervix measured at mid-gestation by transvaginal ultrasound, and a history of preterm birth.[1] Progesterone plays an important role in the menstrual cycle, in maintaining the early stages of pregnancy as well as later in gestation. It acts on the endometrium by converting the proliferative phase induced by oestrogen to a secretory phase. There is increasing evidence to suggest that the onset of labour is preceded by a functional withdrawal of progesterone action at the level of the uterus.[2] Progesterone supplementation has been used to prevent preterm birth, although the exact mechanism by which progesterone may delay birth is not fully understood.[3] Proposed explanations are that progesterone promotes myometrial relaxation, inhibits prostaglandin production and possesses anti-inflammatory properties to counteract the inflammatory process involved in the initiation of labour.[3,4]

There are several strategies with varying levels of evidence to prevent preterm birth in women with a history of spontaneous preterm birth or short cervix. Interventions include vaginal progesterone supplementation, cervical cerclage or cervical pessary. In the United States (US), 17-hydroxyprogesterone caproate (17-OHPC) administered intramuscularly, is approved for progesterone supplementation between 16 to 37 weeks of gestation to reduce the risk of preterm birth in women with a singleton pregnancy and a history of spontaneous singleton preterm delivery.[5] This product is not currently approved in Australia.

Current clinical practice in Australia for the use of progesterone for the prevention of preterm birth is as per the current Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) statement.[6] The consensus-based recommendations presented in the guidance are:

- vaginal progesterone is recommended for asymptomatic women with a short cervix (< 25 mm) on transvaginal cervical length assessment in the midtrimester; and

[1] Dodd, J.M. et al (2013). Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth, *Cochrane Systematic Review - Intervention*, 2013.
[2] Dodd, J.M. et al (2017). Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy, *Cochrane Systematic Review - Intervention*, 2017.
[3] Romero, R. et al (2018). 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: 161-180.
[4] Conde-Agudelo, A. and Romero, R. (2016). Vaginal progesterone to prevent preterm birth in pregnant women with a sonographic short cervix: clinical and public health implications, *Am J Obstet Gynecol*, 2016; 214: 235-242.
[5] United States Prescribing Information for Makena (hydroxyprogesterone caproate injection), 2017.
[6] Royal Australian and New Zealand College of Obstetricians and Gynaecologists, (2017), Statement; Progesterone: Use in the second and third trimester of pregnancy for the prevention of preterm birth, C-Obs 29b, July 2017.

- progesterone therapy should be considered for women with a singleton pregnancy with a history of previous spontaneous preterm singleton birth.

The RANZCOG recommendations are consistent with those for prophylactic vaginal progesterone presented in the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) guidelines which recommend:[7]

- 'Offer a choice of either prophylactic vaginal progesterone or cerclage to women with history of spontaneous preterm birth and short cervix (cervical length < 25 mm on transvaginal ultrasound done between 16 and 24 weeks of pregnancy)'.
- 'Offer prophylactic vaginal progesterone to women with short cervix (< 25 mm on transvaginal ultrasound done between 16 and 24 weeks of pregnancy) and no history of spontaneous preterm birth or mid-trimester loss'.

This literature based submission (LBS) application was to extend the indication for Oripro (progesterone) for prevention of preterm birth in singleton pregnancies at risk due to short cervix or a history of spontaneous preterm birth.

Regulatory status

Oripro (progesterone) received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 8 October 1991 as a 100 mg (ARTG R 21190) and 200 mg (ARTG R 21195) pessary jar for the following indication:

> *Assisted reproductive technology (ART) treatment of infertile women with progesterone deficiency, requiring progesterone supplementation or replacement to support embryo implantation and maintain initial pregnancy.*

The 100 mg (ARTG R 165111) and 200 mg (ARTG R 165112) pessary strip packs were registered on the ARTG on 20 October 2009 for the same indication as the pessary jars.

At the time the TGA considered the application discussed in this AusPAR, a similar application had not been approved in any country.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-04477-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	30 November 2018

[7] United Kingdom (UK) National Institute for Health and Care Excellence (NICE), Guidelines for Preterm labour and birth (NG25), 2015.

Description	Date
First round evaluation completed	30 April 2019
Sponsor provides responses on questions raised in first round evaluation	2 July 2019
Second round evaluation completed	31 July 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	3 September 2019
Sponsor's pre-Advisory Committee response	13 September 2019
Advisory Committee meeting	4 October 2019
Registration decision (Outcome)	6 November 2019
Completion of administrative activities and registration on ARTG	12 November 2019
Number of working days from submission dossier acceptance to registration decision*	189

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The nonclinical dossier was entirely literature based, comprising 17 published papers dating from 1960 to 2016. All submitted papers were reviewed by the nonclinical evaluator, who summarised the following points below.

Nonclinical efficacy

Progesterone was shown to significantly prolong the state of uterine quiescence *in vivo* in ovariectomised non-gravid rats following exogenous administration (2.5 mg/kg intramuscular (IM)), acting to reduce the frequency of uterine contractions and the power of the uterine myoelectrical activity.[8] *In vitro*, progesterone (1 µM) significantly reduced

[8] Celik, O. et al. (2008) Assessment of myoelectrical signal parameters in estrogen, progesterone, and human chorionic gonadotropin administered in nonpregnant rat myometrium after ovariectomy. *Fertil. Steril.* 2008; 89: 188- 198.

spontaneous and oxytocin-induced contractile force and oxytocin-induced (but not spontaneous) contraction frequency in experiments with isolated mouse uterine horns.[9]

A study in pregnant mice investigating the molecular mechanisms by which progestogens may prevent preterm birth did not identify changes in the expression of the set of genes examined (ones known to be involved in uterine contractility/quiescence, or pathways involved in cervical remodelling) following treatment with progesterone in mid-late gestation (1 mg vaginally over gestation days 14 to 17, compared with gestation in the mouse lasting 19 to 20 days).[10] The duration of gestation was reported to be increased in rats treated with progesterone (8.3 mg/kg/day subcutaneous (SC)) beginning on gestation day 15 (to day 26 or longer compared with a normal gestation length of 21 to 23 days in the rat) in a literature report from 1974 cited in a submitted review article.[11]

Developmental toxicity

Data compiled by the sponsor identify adverse effects of progesterone on embryofetal development in *in vivo* studies performed in laboratory animal species: fetal lethality and cleft palate in mice; fetal lethality in rats; and embryo- and fetal lethality and masculinisation (of both sexes) in rabbits.[11,12,13,14] Masculinisation in rabbits occurred with maternal treatment at 30 mg/kg/day IM over gestation days 8 to 16 (compared with the period of organogenesis covering days 7 to 20 of gestation, and gestation lasting 31 to 32 days, in the rabbit). Of particular note, though, masculinisation of female fetuses was not seen in the rat following maternal treatment with progesterone at up to approximately 800 mg/kg/day SC over gestation days 15 to 20 (compared with the period of organogenesis covering days 9 to 17 of gestation, and gestation lasting 21 to 23 days, in the rat).[15] Adjusted for body surface area, the upper dose level employed in this rat study is 36 times higher than the clinical dose for the proposed new indication. Masculinisation of female fetuses was also not observed in the guinea pig, but in this study the tested dose (1 mg/kg over gestational days 18 to 60) is inadequate, being 16.5 times lower than the proposed clinical dose on a body surface area adjusted basis.

Masculinisation with maternal progesterone treatment has also been observed in mice. In a paper retrieved independently by the nonclinical evaluator, increased anogenital distance and aggressive behaviour were reported in the female offspring of pregnant mice treated with 0.25 or 0.5 mg (approximately 1 to 2 mg/kg) progesterone SC on gestation days 12 to 16 (compared with the period of organogenesis covering days 7.5 to 16 of gestation, and gestation lasting 19 to 20 days, in the mouse).[16]

[9] Patil, A. S. et al. (2015) Progesterone Metabolites Produced by Cytochrome P450 3A Modulate Uterine Contractility in a Murine Model. *Reprod. Sci*. 2015; 22: 1577-1586.
[10] Nold, C. et al. (2013) Prevention of preterm birth by progestational agents: what are the molecular mechanisms? *Am. J. Obstet. Gynecol*. 2013; 208: 223.e1–7.
[11] Christian M.S. et al (2007) Embryo-fetal toxicity signals for 17alpha-hydroxyprogesterone caproate in high-risk pregnancies: a review of the non-clinical literature for embryo-fetal toxicity with progestins. *J. Matern. Fetal Neonatal Med.* 2007; 20**:** 89- 112.
[12] Petrelli E.A. and Forbes T.R. (1964) Toxicity of Progesterone to Mouse Fetuses. *Endocrinology.* 1964; 75: 145- 146.
[13] Piotrowski J. (1968) Experimental investigations on the effect of progesterone on embryonal development. Part II. Investigations carried out on rabbits. *Folia Biol (Krakow)*. 1968; 16: 335-342.
[14] Hudson, R., Hemphill, P. and Tillson, S.A. (1978a) Preclinical evaluation of intrauterine progesterone as a contraceptive agent. I. Local contraceptive effects and their reversal. Contraception., 1978a; 17: 465-474.
[15] Revesz, C., Chappel C.I. and Gaudry R. (1960) Masculinization of female fetuses in the rat by progestational compounds. *Endocrinology*. 1960; 66: 140-144.
[16] Wagner, C.K., Kinsley C. and Svare B. (1986) Mice: postpartum aggression is elevated following prenatal progesterone exposure. *Horm. Behav*. 1986; 20: 212–221.

Administration of progesterone during pregnancy (3.3 mg/kg/day from gestation day 7) was found to increase monoamine oxidase (MAO) activity in the fetal rat brain.[17] The functional significance is unclear.

There was an accompanying increase in fetal mortality in the study referred to above under nonclinical efficacy reporting an increase in the duration of gestation in rats treated with progesterone in late pregnancy (from a literature report from 1974 cited in Christian et al., 2007).[11]

It must be borne in mind, as Christian et al. (2007);[11] themselves note, that none of the identified developmental toxicity studies with progesterone meets current standards for determining reproductive and developmental effects as part of the process of drug development.

Conclusions and recommendations

- Nonclinical data offer support for efficacy in the treatment of preterm birth.
- Animal studies identify the potential for progesterone to cause adverse effects on embryofetal development, most notably related to genital malformation. These, though, are seen to be dependent on the time of treatment. Although the available data are limited, adverse effects on embryofetal development were not encountered in laboratory animal species with treatment with progesterone solely during the later stages of pregnancy up to delivery, apart from increased fetal mortality that was secondary to progesterone's desired action to delay parturition, observed in rats.
- Given the additional availability of clinical data relevant to use in pregnancy, there are no nonclinical objections to the proposed extension of indication for Oripro provided the identified clinical benefits outweigh the risks.
- The sponsor has adopted all of the PI changes recommended in the nonclinical evaluation report and the non-clinical evaluator has confirmed acceptance of the PI.

Clinical

The clinical evaluator has recommended approval of Oripro (progesterone) for the proposed indication and dosage regimens.

Pharmacology

Pharmacokinetics

No new pharmacokinetics (PK) data is presented.

Pharmacodynamics

The pharmacodynamics (PD) publications included both *in vivo* and *in vitro* evaluations and provided preliminary evidence to suggest possible mechanisms by which progesterone may prevent preterm birth: by improving uterine and foetal circulation (significant reduction in pulsatility index and resistance index (RI)) later in gestation in singleton pregnancies;[18,19] inhibits connexin 43 expression leading to a reduced ability of the uterus to contract as a syncytium and reduces neutrophil cluster of differentiation 11b

[17] Snyder, A.M., Hull, E.M. and Roth, J.A. (1979), The effect of maternal progesterone injections on fetal development of brain monoamine oxidase of rats. *Brain Res*. 1979; 170: 194-197.
[18] Abd El Hameed, A.A. (2012), Vaginal versus intramuscular progesterone in the prevention of preterm labor and their effect on uterine and fetal blood flow, Middle East Fertil. Soc. J, 2012; 17: 163-169.
[19] Barda, G. et al. (2010), Effect of vaginal progesterone, administered to prevent preterm birth, on impedance to blood flow in fetal and uterine circulation, *Ultrasound Obstet Gynecol*, 2010; 36: 743–748.

(CD11b) expression leading to a reduction in leukocyte migration to the myometrium.[20] The clinical results of the STOPPIT study (tissues from patients in this study were used in the Norman (2011) study);[20] have been published and showed that progesterone did not prevent preterm delivery in women with twin pregnancy.[21]

Overall, no definitive conclusions regarding the mechanism of action of vaginal progesterone for the prevention of preterm birth could be made based on the limited data from the 5 PD studies.

Efficacy

The review of the literature identified 26 publications to support the current submission. The following studies were discussed in the clinical evaluation report to address the efficacy of Oripro in the proposed indication:

- seven meta-analyses/systematic reviews;[1,2,3,22,23,24,25]
- four individual randomised controlled trials;[26,27,28,29] and
- two other efficacy studies.[30,31]

All meta-analyses included in the application used preterm births as a primary end point, predominately preterm birth less than 33 or 34 weeks gestation. Dodd et al., (2017);[2] and Velez-Edwards et al., (2013);[25] also included neonatal death as a primary outcome. The secondary outcome measures used in the meta-analyses, and to a lesser extent the individual studies, represent a wide range of parameters relevant to both maternal and neonatal outcomes.

Singleton pregnancies

Norman et al., (2016) (also known as the OPPTIMUM study);[29] was a multicentre, randomised double blind placebo controlled trial, and was one of the largest studies to

[20] Norman, J.E. (2011), Effect of prolonged in vivo administration of progesterone in pregnancy on myometrial gene expression, peripheral blood leukocyte activation, and circulating steroid hormone levels, *Reproductive Sciences*, 2011; 18: 435-446.
[21] Norman, J.E. et al. (2009). Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. *Lancet.* 2009; 373: 2034-2040.
[22] Jarde, A. et al. (2017a), Preterm birth prevention in twin pregnancies with progesterone, pessary, or cerclage: a systematic review and meta-analysis, *BJOG*, 2017a; 124: 1163–1173.
[23] Jarde, A et al. (2017b), Effectiveness of progesterone, cerclage and pessary for preventing preterm birth in singleton pregnancies: a systematic review and network meta-analysis, BJOG, 2017b; 124: 1176–1189.
[24] Romero, R. et al. (2017), Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data, *Ultrasound Obstet Gynecol* 2017; 49: 303–314.
[25] Velez Edwards, D.R. et al. (2013), Progestogens for preterm birth prevention: a systematic review and meta-analysis by drug route, *Arch Gynecol Obstet*, 2013; 287: 1059–1066.
[26] Brizot, M.L. et al (2015), Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol*, 2015; 213: 82.e1-9
[27] Rode, L. et al. (2011), Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone, *Ultrasound Obstet Gynecol*, 2011; 38: 272–280.
[28] Bafghi, A.S.T, Bahrami, E. and Sekhavat, L. (2015), Comparative study of vaginal versus intramuscular progesterone in the prevention of preterm delivery: a randomized clinical trial, *Electronic Physician*, 2015; 7: 1301-1309.
[29] Norman, J.E. et al. (2016), Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial, Lancet, 2016; 387: 2106-2116.
[30] Klein, K. et al. (2011), Vaginal micronized progesterone and risk of preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis, *Ultrasound Obstet Gynecol*, 2011; 38: 281–287.
[31] Van Os, M.A. et al. (2015), 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, Am J Perinatol, 2015; 32: 993-1000.

compare obstetric, neonatal, and childhood outcomes in high-risk women with singleton pregnancy treated with vaginal progesterone to prevent preterm birth. The patient population evaluated in this study represented the target patient population (80% had history of spontaneous preterm birth and 34 to 38% had cervical length < 25mm), and also evaluated the proposed vaginal progesterone dose and formulation (200 mg progesterone daily). Overall compliance was only 69%. The participant administered the vaginal study medication daily at bedtime, commencing from about 22 to 24 weeks of gestation until 34 weeks or delivery of the baby, whichever was sooner.

Vaginal progesterone was not associated with reduced risk of preterm birth or composite neonatal adverse outcomes, and had no long-term benefit or harm on outcomes in children at 2 years of age. Although no overall effect was observed, point estimates of the reduction in the odds of the obstetric outcome (0.86) and the neonatal composite outcome (0.62) suggested benefit with progesterone, but with confidence intervals (CIs) that showed no statistically significant difference.

The Romero et al., (2018) systematic review and meta-analysis;[3] provides the main evidence for efficacy of vaginal progesterone in prevention of preterm birth in women with singleton pregnancy and at risk of preterm birth. This included individual patient data from 5 randomised controlled trials which compared vaginal progesterone (any dose) with placebo/no treatment in 974 women with singleton pregnancy and midtrimester sonographic short cervix < 25 mm. The daily dose of vaginal progesterone used in the trials varied from 90 to 200 mg and the treatment was administered from 18 to 25 weeks to 34 to 36 weeks of gestation.

Vaginal progesterone was associated with a significant reduction in the risk of preterm birth < 33 weeks of gestation (relative risk (RR) = 0.62; 95% CI: 0.47, 0.81; p = 0 .0006; high-quality evidence). The frequencies of preterm birth < 36, < 35, < 34, < 32, < 30 and < 28 weeks of gestation were also significantly lower in the vaginal progesterone group. Treatment with vaginal progesterone was also associated with a significant reduction in the risk of respiratory distress syndrome (RDS), composite neonatal morbidity and mortality, birth weight < 1500 and < 2500 g, and admission to the neonatal intensive care unit (NICU; RRs from 0.47 to 0.82). This meta-analysis also showed a beneficial effect of vaginal progesterone across a range of subgroups, including patients with or without a previous spontaneous preterm birth. There was no difference in efficacy in the prevention of preterm birth when either 90 to 100 or 200 mg/day of vaginal progesterone was administered. Of the 5 main randomised controlled trials which contributed data for this meta-analysis, it is noted that the proposed dose of 200 mg vaginal progesterone was only used in the Fonseca et al., (2007);[32] and the Norman et al., (2016);[29] studies. Cetignoz et al., (2011);[33] showed reduction in risk of preterm birth as well as improved perinatal outcomes with 100 mg vaginal progesterone while the other studies evaluated vaginal progesterone gel.[34,35] Overall, the Romero et al., (2018) individual patient data meta-analysis;[3] provided Level I evidence that vaginal progesterone in pregnant women with singleton pregnancy and short cervical length ≤ 25 mm reduces the risk of preterm birth from < 28 to < 36 weeks of gestation and reduces the risk of adverse neonatal outcomes.

[32] Fonseca, E.B. et al (2007). Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med*. 2007; 357: 462–469.
[33] Cetingoz, E. et al (2011), Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. *Arch Gynecol Obstet*. 2011; 283: 423–429.
[34] O'Brien, J.M. et al. (2007), Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol*. 2007; 30: 687–696.
[35] Hassan, S.S. et al. (2011), Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol*. 2011; 38: 18–31.

Fonseca et al., (2007);[32] was a randomised, double blind, placebo controlled trial that examined the effects of vaginal progesterone on the prevention of preterm birth in women with a short cervix (transvaginal ultrasonography at a median of 22 weeks of gestation) conducted at King's College Hospital Medical School, London, UK. Cervical length was < 15 mm in 413 of the women (1.7%), and 250 (60.5%) of these 413 women were randomly assigned to receive vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks of gestation. The primary outcome was spontaneous delivery before 34 weeks.

Progesterone administration significantly reduced the rate of spontaneous preterm birth before 34 weeks by about 44% (19.2% versus 34.4% in controls; RR = 0.56, 95% CI: 0.36 to 0.86). Progesterone was associated with a non-significant reduction in neonatal morbidity (8.1% versus 13.8%; RR = 0.59, 95% CI: 0.26 to 1.25; p = 0.17). There were no serious adverse events associated with the use of progesterone.

Cetignoz et al., (2011);[33] was a randomised, double blind, placebo controlled study that included 150 high risk pregnancies. This study showed significant reduction in incidence of preterm birth < 37 weeks and < 34 weeks in women with high risk pregnancies (including prior spontaneous preterm birth, twin pregnancy) following treatment with vaginal progesterone suppository (100 mg daily) between weeks 24 and 34 of gestation.

The network meta-analysis by Jarde et al., (2017);[23] compared progesterone (either natural progesterone per vagina or orally; or IM 17-OHPC), cervical cerclage and pessary to determine their relative effects in women with singleton pregnancies at risk of preterm birth. Of the 36 studies included in this meta-analysis, a control group of usual care or placebo was compared with progesterone (IM and intravaginal) in 17 studies and showed that progesterone (particularly vaginal progesterone) was effective in reducing risk of preterm birth in at-risk women with a singleton pregnancy. Although the quality of evidence ranged from very low to high, progesterone decreased preterm birth < 34 weeks, < 37 weeks and other effects of preterm birth including neonatal death. However, evidence for proposed intravaginal progesterone (200 mg daily) was limited to 3 studies;[29],[32],[31],and only the Fonseca et al., (2007) study;[32] showed significant reduction in preterm birth < 37 weeks, while the other studies failed to show significant reduction for preterm birth (< 37 weeks or < 34 weeks). In subgroup of women with previous preterm birth, progesterone was associated with significant reduction in preterm birth < 34 weeks (odds ratio (OR) = 0.44, 95% CI: 0.28, 0.69) with similar results for preterm birth < 37 weeks (of the 8 studies included in this subgroup analysis, only Fonseca et al., (2007);[32] evaluated the proposed 200 mg vaginal progesterone). Subgroup analysis in women with cervix < 25 mm also showed significant reduction in preterm birth < 34 weeks and preterm birth < 37 weeks.

Systematic reviews by Dodd et al., (2013);[1] and Velez- Edwards et al., (2013);[25] included analyses of studies in both singleton and multiple pregnancies. However, results showed that reduction in risk of preterm birth and other neonatal outcomes following treatment with vaginal progesterone was limited to women with singleton pregnancies at risk of preterm birth (specifically with past history of spontaneous preterm birth and with short cervix). Both meta-analyses failed to show significant reduction in risk of preterm birth and perinatal deaths in women with multiple pregnancies.

The Bafghi et al., (2015) study;[28] in women with singleton pregnancy at risk of preterm birth (history of preterm delivery or a short cervix < 25 mm measured by transvaginal ultrasound) did not show any significant difference in prevention of preterm birth when intravaginal progesterone (200 mg daily) was compared with only other treatment approved (in the US only) for prevention of preterm birth (17-OHPC 250 mg IM weekly). However, interpretation of results was limited by lack of placebo/control group.

The Van Os et al., (2015) study;[31] failed to show statistically significant benefit of vaginal progesterone in reducing composite adverse neonatal outcome and preterm birth in

women with low risk singleton pregnancy and a short cervix < 30 mm. The study was underpowered due to a much lower than anticipated number of women with short cervix and was stopped early because of this. Furthermore, the subjects evaluated in this study did not include the target patient population, that is, women with history of preterm birth or cervical length < 25 mm.

Twin pregnancies

Romero et al., (2017);[24] was an updated systematic review and meta-analysis of individual patient data (IPD) from 6 randomised controlled trials comparing vaginal progesterone with placebo/no treatment in 303 women with a twin gestation and a mid-trimester sonographic cervical length ≤ 25 mm. Results of this meta-analysis provided moderate level evidence that administration of vaginal progesterone to asymptomatic women with a twin gestation and a sonographic short cervix in the mid-trimester reduces the risk of preterm birth occurring at < 30 to < 35 gestational weeks, neonatal mortality and some measures of neonatal morbidity. This was the only submitted study/meta-analysis in women with twin/multiple gestations that showed some evidence of efficacy of vaginal progesterone in proposed indication. However, interpretation was confounded by fact that only two trials included in this meta-analysis were specifically designed to assess the efficacy of vaginal progesterone in women with a twin gestation and a sonographic short cervix. Furthermore, about 74% of the total sample size of the IPD meta-analysis was provided by one study, which was not placebo-controlled and used 400 mg daily vaginal progesterone.

Jarde et al., (2017);[22] was a systematic review included 23 trials comprising 6626 women with twin pregnancies of which 7 studies provided results on effects of intravaginal progesterone on preterm birth and showed that intravaginal progesterone did not result in significant reduction in preterm birth in twin gestations. Although intravaginal progesterone did improve some important secondary outcomes, interpretation was limited by fewer studies evaluating these outcomes and wider confidence intervals.

In the Dodd et al., (2017) meta-analysis,[2] the administration of progesterone (either IM or vaginal) was not associated with a reduction in risk of preterm birth or improved neonatal outcomes in women with a multiple pregnancy (included 17 randomised controlled trials which compared either vaginal or intramuscular progesterone with a placebo or no treatment, and involved a total of 4773 women). Systematic reviews by Dodd et al., (2013);[1] and Velez-Edwards et al., (2013);[25] included analyses of studies in both singleton and multiple pregnancies and both these meta-analyses failed to show significant reduction in risk of preterm birth and perinatal deaths in women with multiple pregnancy.

Two individual studies, Brizot et al., (2015);[26] and Rode et al., (2011);[27] (and its secondary analysis, Klein et al., (2011)[30]) focused on twin/multiple pregnancies and none of these studies provided evidence to support use of intravaginal progesterone for prevention of preterm birth. In fact, the Klein et al., (2011) secondary analysis of the Rode et al., (2011) study (which was one of the largest trials to investigate effect of progesterone treatment on prevention of preterm birth in twin gestations) concluded that there is no justification for prophylactic use of progesterone in high risk twin pregnancies.

Safety

The safety for vaginal progesterone in proposed indication was supported from 9 meta-analyses and 10 individual studies. The safety population comprised of women, with a mean age of approximately 30 to 32 years with singleton or multiple pregnancies. The safety data set includes five studies in singleton pregnancies, nine studies in twin pregnancies and five studies which reported outcomes for single and multiple pregnancies.

Safety results were mainly presented as:

- maternal (obstetric) outcomes;
- perinatal and neonatal outcomes; and
- long term childhood outcomes.

The dose of progesterone ranged from 90 mg to 400 mg given vaginally once a day. A variety of progesterone dose forms and formulations were used, including gel (Crinone vaginal progesterone gel), soft capsules (vaginal progesterone) and conventional pessaries.

There were a limited number of literature studies reviewing progesterone for the prevention of preterm birth reported adverse events (AE). However, in those trials that did report on the incidence and nature of treatment-related AEs, these were generally mild and transient, and the incidence of AEs was no greater than those reported for placebo or no treatment.

Maternal (obstetric) outcomes

Maternal safety was not reported consistently across submitted studies. In the studies which reported maternal outcomes, there were no clear differences between the vaginal progesterone and placebo groups.[1,3,23,27,30,31] There were no trials in the safety data set which reported maternal mortality. A few studies reported AEs such as vaginal pruritus, vaginal discharge, vaginal candidiasis and nausea although the incidence of these events was comparable to placebo.[23,27,31] These AEs are consistent with the general use of vaginal progesterone and the approved Oripro PI.

Perinatal and neonatal outcomes

The most commonly reported AEs in the studies investigating neonatal safety was neonatal death, Apgar score < 7 at 5 min;[36] and birth weight, requirement for supportive care such as use of mechanical ventilation and admission to the NICU. There was some evidence to indicate that vaginal progesterone significantly reduced the risk of a number of the neonatal outcomes: neonatal death;[22,23,24,25] composite neonatal morbidity and mortality;[3,37] very low birth weight;[3,23,24] use of mechanical ventilation; [2,24] and admission to NICU.[3,23]

Long terms childhood outcomes

Four studies assessed longer-term outcomes in infants or children:

- Klein et al., (2011);[30] did not observe a difference in neurophysiological development of twins assessed at 6 and 18 months using the validated Ages and Stages Questionnaire (ASQ) completed by the parents.
- Vedel et al., (2016);[38] observed a statistically higher mean total ASQ score in twins exposed to progesterone in utero at 48 to 60 months relative to placebo. An increased risk for a heart related diagnosis in dichorionic twins exposed prenatally to progesterone was observed in a subgroup analysis. Children exposed in utero to progesterone did not show a difference in the rates of clinical diagnoses, hospital admissions and length of hospital stay compared with placebo up to 8 years of age.

[36] The Apgar is a quick five criteria score used to evaluate the newborn baby against infant mortality. Each criteria (skin colour (appearance), pulse rate, grimace irritability reflex, muscle tone (activity) and respiratory effort) is scored on a scale of zero to two. The resulting Apgar score is calculated by the summing up of the five scores, to produce a total score of between zero and ten. An Apgar score of 7 more at 5 minutes after birth indicates that the baby is adapting well to the environment.
[37] Fox, N.S et al. (2016), Cervical Pessary and Vaginal Progesterone in Twin Pregnancies With a Short Cervix, *Obstet Gynecol*, 2016; 127: 625-630.
[38] Vedel, C. et al (2016), Long-term effects of prenatal progesterone exposure: neurophysiological development and hospital admissions in twins up to 8 years of age, *Ultrasound Obstet Gynecol* 2016; 48: 382–389.

- McNamara et al., (2015);[39] observed no difference between children exposed to progesterone in utero and placebo group in child deaths, congenital malformations and health service utilisation (following review of health records) and also in social, emotional and cognition development (based on validated parent questionnaire follow up at 55.5 months).
- Norman et al., (2016);[29] observed no differences in the cognitive function of singletons exposed to progesterone in utero and placebo at two years of age based on Bayley-III cognitive composite score.[40]

No deaths or abnormalities at birth and no side effects were observed in the only study that compared vaginal and IM progesterone supplementation for prevention of preterm birth in women with singleton pregnancy.[28]

A search of the Database of Adverse Notifications was conducted for available post-marketing safety information with 34 reported adverse events across all of the vaginally administered progesterone products over a long period (1991 to 2018) and no new safety concerns were identified.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[41]

Risk-benefit analysis

Delegate's considerations

Nonclinical

In relation to the nonclinical evaluation,

- the sponsor has adopted all of the PI changes recommended in the nonclinical evaluation report and the nonclinical evaluator has confirmed acceptance of the PI.

Efficacy

Based on the submitted literature reviews and investigator-sponsored studies, there is evidence to support the efficacy of vaginal progesterone use for the proposed indication of prevention of preterm birth in women with singleton pregnancy that have a short cervix and/or history of spontaneous preterm birth. However, there is lack of adequate evidence for efficacy of proposed vaginal progesterone for prevention of preterm birth in pregnant women with twins/multiple gestation who have a short cervix or history of spontaneous preterm birth.

Different progesterone preparations, routes of administration and dosage were also evaluated in the submitted studies. The majority of the pivotal studies (and the studies included in the meta-analyses) evaluated the proposed 200 mg daily dose of intravaginal progesterone. Overall, the 200 mg dose has been shown to have as efficacious and similar risk/benefit profile to that of the lower 90 to 100 mg dose. The sponsor rationalises the

[39] McNamara, H.C. et al (2015), STOPPIT Baby Follow-Up Study: The Effect of Prophylactic Progesterone in Twin Pregnancy on Childhood Outcome, PLOS ONE, 2015; 10: e0122341.
[40] Bayley III (2006): The Bayley Scales of Infant and Toddler Development, (Third Edition) is an individually administered assessment of the developmental functioning of infants, toddlers, and young children from 1 to 42 months of age. It is comprised of the following five domains: cognitive, language, motor, adaptive, and social-emotional development.
[41] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

proposed dose being supported by the widespread use of 200 mg progesterone in Australian clinical practice and the extra weightage of 200 mg vaginal progesterone in the studies/meta-analysis than other dosages. The proposed dose of 200 mg for prevention of preterm labour in the proposed indication appears appropriate. This is for discussion at the Advisory Committee on Medicines (ACM).

Various definitions were used for 'short cervical length' ranging from < 30 mm to < 15 mm. However, majority of the studies used definition of ≤ 25 mm or < 25 mm (including the pivotal Romero et al., (2018) meta-analyses).[3] Is the proposed definition of < 25 mm, in the PI, appropriate? This is for discussion at the ACM.

Timing of therapy has also varied between studies, stating as early as 16 weeks of gestation in women with a previous history of spontaneous preterm delivery and continuing to 37 weeks in some trials. Treatment with vaginal progesterone was generally started at some time during second trimester of pregnancy (that is, from 16th to 24th week) in most of the studies and treatment was continued into the third trimester (34th or 36th week or until delivery). The proposed dosing period is similar to above and appears appropriate. This is for discussion at the ACM.

Safety

Overall, the submitted literature reviews demonstrated that the use of proposed vaginal progesterone for prevention of preterm birth in women did not increase the risk of maternal or perinatal mortality/ morbidity outcomes as compared to placebo (comparable for singleton and multiple pregnancies). No safety signals were identified for vaginal administration of progesterone for proposed indication.

Data deficiencies

Progesterone crosses the placenta. No association has been found between the maternal use of progesterone in early pregnancy and fetal malformations. However, the data on the risk of fetal effects (short and long term) with exposure in later stages (second and third trimesters) of pregnancy (as for the proposed indication) is still limited and should be listed as missing information (by the sponsor) in the Australian specific Annex (ASA) of the risk management plan (RMP) for Oripro;[42] and followed up as part of Oripro pharmacovigilance activities.

In the US, 17-OHPC administered IM, is approved for progesterone supplementation between 16 to 37 weeks of gestation to reduce the risk of preterm birth in women with a singleton pregnancy and a history of spontaneous singleton preterm delivery. Currently, no intravaginal progesterone formulations are registered for the prevention of preterm birth either in Australia or overseas. Hence, the proposed vaginal progesterone provides a therapeutic option for prevention of preterm birth in women with singleton pregnancy at high risk of preterm birth due to short cervix or history of spontaneous birth with potential benefits for both the infant and mother.

Summary

Overall, the benefit risk balance for use of Oripro (200 mg vaginal progesterone daily) in the proposed indication appears favourable although advice is sought from the committee regarding the issues raised above.

Proposed action

The Delegate has no reason to say, at this time, that the application for Oripro should not be approved for registration.

[42] There was no risk management plan for this particular submission.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Is the definition of short cervix, of < 25 mm, appropriate?
2. Is the proposed dose 200 mg the most appropriate dose for the *'Prevention of preterm birth'* indication?
3. Is the proposed dosing period appropriate?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee considerations[43]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Oripro vaginal pessaries, containing 100 mg and 200 mg of progesterone.

The ACM considered this product to have an overall positive benefit-risk profile for the proposed indication:

> *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 birth.*

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice.

1. Is the definition of short cervix, of < 25 mm, appropriate?

The ACM was of the view that the definition of short cervix should be revised to include cervical length of equal to or less than 25 mm.

2. Is the proposed dose 200 mg the most appropriate dose for the 'prevention of preterm birth' indication?

The ACM acknowledged that while lower doses of progesterone have been used effectively for this indication, the proposed dose is the most widely used, would be already familiar to clinicians and poses no safety concerns.

3. Is the proposed dosing period appropriate?

The ACM noted the variability of the dosing periods used in clinical practice in Australia and internationally. Overall, the ACM was of the view that the currently proposed dosing

[43] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

period was appropriate: 'Treatment can be initiated during the second trimester (16 to 24 weeks gestation) and is to be continued to the end of the 36th week of gestation or until delivery'.

4. ***The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.***

The ACM identified no further issues of concern.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Oripro (progesterone) 100 mg and 200 mg vaginal pessary, for the following extension of indications:

Oripro Pessaries are indicated for 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.*

As such, the full indications at this time were:

Oripro Pessaries are indicated for:

- *Assisted reproductive technology (ART) treatment of infertile women with progesterone deficiency, requiring progesterone supplementation or replacement to support embryo implantation and maintain initial pregnancy.*
- *Prevention of preterm birth in singleton pregnancies at risk due to;*
  - *Shortened cervix (midtrimester sonographic cervix ≤ 25mm)*

    and/or

  - *Where there is a history of spontaneous preterm birth.*

Specific conditions of registration applying to these goods

This approval does not impose any requirement for the submission of periodic safety update reports. The sponsor should note that it is a requirement that all existing requirements for the submission of periodic safety update reports as a consequence of the initial registration or subsequent changes must be completed.

Attachment 1. Product Information

The PI for Oripro approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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