Attachment 1: Product information for AusPAR - ORIPRO - Progesterone - Orion Laboratories Ltd (T/A Perrigo Australia) - PM-2018-04477-1-5 FINAL 7 February 2020. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

AUSTRALIAN PRODUCT INFORMATION – ORIPRO® (PROGESTERONE) PESSARIES

1 NAME OF THE MEDICINE

Progesterone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oripro Pessaries contain as active substance 100mg or 200mg of progesterone (micronized) in hard fat.

3 PHARMACEUTICAL FORM

Vaginal Pessaries - Opaque, bullet-shaped waxy, solid masses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Oripro Pessaries are indicated for:

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

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The dosage of progesterone for prevention of preterm birth is 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.

Other intravaginal therapies should not be used while progesterone pessary treatment is being undertaken.

The pessary should be removed from its wrapper and inserted deep into the vagina, while either in a squatting position or lying on back or side. If a daily dose is being administered then a preferable time of dosing is at night before retiring.

A missed dose should be administered as soon as remembered, unless the missed dose is noticed at the day of the next dose. In the latter case the missed dose should be omitted and the regular dosing regimen continued.

4.3 CONTRAINDICATIONS

- Sensitivity to progesterone, sensitivity to hard fat
- Undiagnosed vaginal bleeding
- Undiagnosed urinary tract bleeding
- Liver dysfunction or disease
- Active thrombophlebitis or thromboembolic disorder (deep vein thrombosis pulmonary embolism) or a history of hormone associated thrombophlebitis or thromboembolic disorder
- Known or suspected malignancy of the breast or genital organs
- Missed abortion or ectopic pregnancy

Progesterone is contraindicated in pregnancy during assisted reproductive technology (ART) treatment, when normal progesterone levels are present.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Before initiation or recommencing progesterone therapy in women, a physical examination should be performed, including special attention to the breasts, abdomen and pelvic organs and a Papanicolaou (Pap) smear.

Conditions that might be aggravated by fluid retention (e.g. asthma, seizure disorders, migraine, or cardiac or renal dysfunction).

History of mental depression; discontinue if serious depression recurs during therapy.

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Diabetic patients as high doses of progesterone therapy can lower glucose tolerance in some patients.

Hyperlipidemia as progesterone may increase low density lipoprotein (LDL) and lower high density lipoprotein (HDL) levels and aggravate problems in controlling hyperlipidemia.

There is consistent evidence from several clinical trials and meta-analysis that supplementation with vaginal progesterone does not reduce risk of preterm birth or improve perinatal outcome in women with twin/multiple gestations. Efficacy and safety in pregnancies with 'threatened preterm labour" or 'other" risk factors for preterm birth has not been established.

Use in hepatic impairment

Use with caution and careful monitoring – History of hepatic disease or dysfunction as progesterone is metabolised in the liver.

Use in the elderly

There is no relevant use in the elderly.

Paediatric use

There is no relevant use in paediatrics.

Effects on laboratory tests

Potentially clinical significant alterations to laboratory test results/values can occur with the following tests:

- Biopsy - (pathologist should be notified of relevant specimens).
- Glucose tolerance test - (varies with progestogens and dose, glucose tolerance may be increased or decreased).
- Metyrapone - (lower response than normally expected).

Apolipoprotein A, HDL, LDL and Total cholesterol and Triglycerides - (serum concentrations may be increased or decreased and may differ depending on type of progestogen, dose, dosing, and duration of therapy).

Liver, thyroid and other endocrine function tests may be affected by progesterone. Coagulation tests: Prothrombin, clotting factors II, VII, VIII, IX, and X - (serum concentrations may be increased).

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4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions with other medicines

Potentially clinically significant interactions with progesterone, may occur with any of the following medications depending on, amount present:

- Hepatic enzyme inducing medications, such as Carbamazepine, Phenobarbitone, Phenytoin, Rifabutin, Rifampicin, may decrease the efficacy of progesterone because of the enhanced liver metabolism caused by these drugs.
- Aminoglutethimide may significantly lower serum concentrations of progesterone by an undetermined mechanism.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would impair fertility until the cessation of treatment.

Use in pregnancy – Pregnancy Category A

Progesterone crosses the placenta. No association has been found between the maternal use of progesterone in early pregnancy and fetal malformations. Male and female genital abnormalities (hypospadias and virilisation) have been observed in fetuses of animals treated with progesterone during gestation, dependent on the time of treatment. Although the available data are limited, adverse effects on embryofetal development were not encountered in laboratory animal species treated with progesterone solely during the later stages of pregnancy up to delivery, apart from an increase in the duration of gestation and an associated increase in fetal mortality.

Use in lactation

Progesterone is excreted into human milk and at supraphysiological levels may affect the quantity of the breast milk. The effect of exogenous progesterone on breast-feeding infants have not been adequately determined in humans. Therefore, Oripro should not be used during lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Use caution when driving a motor vehicle or operating machinery as dizziness or drowsiness may occur.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

As Progesterone pessaries are being absorbed by mucosal surfaces local irritation or itching may occur in sensitive persons at initiation of treatment, in general this is of a transient nature.

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Overall, the adverse effects observed in women for the ART indication are similar to those for the prevention of preterm birth as follows:

Common (usually dose related)

: Amenorrhoea, abnormal breakthrough uterine bleeding or metromenorrhagia, spotting, changes in cervical eversion and secretions.

: Hyperglycaemia (dry mouth, frequent urination, loss of appetite, unusual thirst).

Uncommon

Galactorrhoea.

Mental depression.

Skin rash, Pruritus.

Rare

Adrenal suppression or insufficiency (causing symptoms of dizziness, nausea or vomiting, unusual tiredness or weakness).

Thromboembolism or thrombus formation (causing headache or migraine, loss of or change of speech, coordination or vision, pain or numbness in chest, arm or leg; unexplained shortness of breath).

For further information, see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use.**

Other

The following additional reactions indicate need for medical attention only if they continue or are troublesome.

: Abdominal cramping, bloating, oedema (swelling face, ankles and feet), unusual tiredness or weakness or weight gain, pain, itchiness or irritation at site of insertion.

: Headache, dizziness, and drowsiness.

: Ovarian enlargement or ovarian cyst formation (abdominal pain), Moniliasis Genital.

: Acne, breast pain or tenderness, hot flushes.

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: Loss or gain of body facial or scalp hair or melasma (brown spots on exposed skin).

: Insomnia

: Nausea.

: Increased blood pressure in susceptible individuals.

: Mild mood changes, nervousness, changes in libido.

Preventative progesterone treatment in women with a history of preterm birth or short cervical length was not associated with increased risk of maternal or perinatal mortality / morbidity outcomes relative to placebo in all analysed progestogen types and pregnancy conditions. Use of vaginal progesterone during second and third trimester of pregnancy for prevention of PTB did not appear to have any effect on long-term childhood outcomes including neurodevelopmental delay. (See Section 5.1 Pharmacodynamic properties, Clinical Trials.)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Overdosage with Oripro Pessaries after vaginal administration is unlikely. If large quantities of pessaries are ingested, euphoria, or nausea, vomiting or dysmenorrhoea may develop.

Treatment

No specific antidote is known. Symptomatic and supportive treatment can be given if necessary.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Progesterone is a naturally occurring female sex hormone secreted by the ovary, placenta and adrenal gland. It acts on the endometrium by converting the proliferative phase induced by oestrogen to a secretory phase. In normal physiological conditions if a released mature ovum is not fertilised a sudden decline in the release of progesterone from the corpus luteum occurs, usually at the end of

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the cycle. However, if fertilisation occurs progesterone is continued to be secreted and the increased level sustains the endometrium and maintains the pregnancy.

Clinical trials

Efficacy data submitted in support of vaginal progesterone as a treatment for the prevention of preterm birth (PTB) in women with a shortened cervix, or where there is a history of spontaneous birth, was provided as published literature. The data consisted of 7 meta-analyses and three clinical trials.

Two systematic reviews, Jarde 2017 and Romero 2018, and an individual trial, Bafghi 2015 focused on the use of progesterone for prevention of PTB in singleton pregnancies. Three systematic reviews, Jarde 2017, Romero 2017 and Dodd 2017, and two individual studies Brizot 2015 and Rode 2011 focused on twin/multiple pregnancies. The systematic reviews by Dodd 2013 and Velez- Edwards 2013 were analyses of studies in both singleton and multiple pregnancies.

All seven meta-analyses used PTB as a primary end point, predominately less than 33 or 34 weeks gestation. Dodd 2013, also used the incidence of major neurodevelopment handicap at 6, 12 and 24 month childhood follow up, with Dodd 2017 and Velez-Edwards 2013 also including neonatal death as a primary outcome. Dodd 2017, additionally included maternal mortality.

Two of the 4 individual clinical trials (Bafghi 2015 and Brizot 2015) used mean gestational age as the primary end point, whilst Rode 2011 and Klein 2011 used PTB <34 weeks gestation.

The meta-analyses by Romero 2017 and 2018, Dodd 2013 and 2017, and Jarde 2017 were considered pivotal evidence. The main efficacy outcomes provided by these studies are summarised below.

Romero 2018, is a systematic review and meta-analysis designed to assess the efficacy of vaginal progesterone in reducing the risk of PTB and adverse perinatal outcomes in asymptomatic women with a singleton pregnancy. Data were available from 974 women (498 allocated to vaginal progesterone, 476 allocated to placebo) with a cervica
high-quality randomised controlled trials (RCT). The daily dose of vaginal progesterone used in the studies varied from 90-200 mg and the treatment was administered from 18-25 to 34-36 weeks gestation.

Vaginal progesterone was associated with a significant reduction in the risk of PTB < 33 weeks gestation (Relative Risk (RR) 0.62; 95%, Confidence Interval (CI) 0.47-0.81; P =.0006). Moreover, vaginal progesterone significantly decreased the risk of PTB at <36, <35, <34, <32, <30, and <28 weeks gestation; spontaneous PTB <33 and <34 weeks gestation; respiratory distress syndrome; composite neonatal morbidity and mortality; birthweight <1500 and <2500 g; and admission to the neonatal intensive care unit (RR from 0.47-0.82).

reduction of neonatal mortality (by 66%, P=0.07) and use of mechanical ventilation (by 35%, P=0.06).

differences in cognitive scores or the frequency of neurodevelopmental impairment or renal, gastrointestinal, and respiratory morbidity between children exposed prenatally to vaginal progesterone vs placebo.

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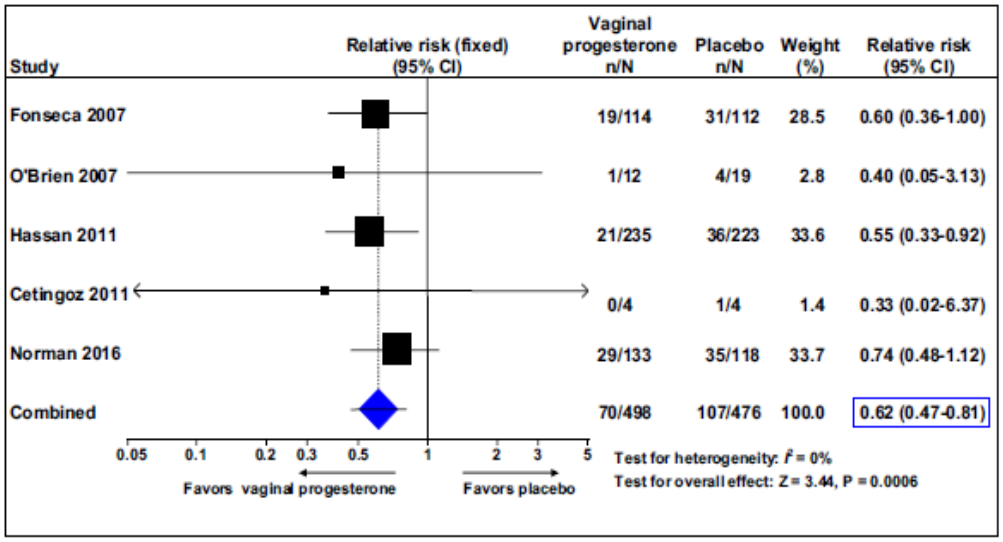
uency of maternal adverse events and congenital anomalies between the vaginal progesterone and placebo groups.

Romero 2018, demonstrated no difference in the efficacy of 90 to 100 mg and 200 mg progesterone in preventing PTB. The relative risk for the lower dose range (n=497), compared to placebo was 0.53 (95% CI 0.33 to 0.87), while for the 200 mg group (n=477) the RR was 0.67 (95% CI 0.49 to 0.93). The interaction value was not significant (p=0.51).

Table 1 - Effect of vaginal progesterone on PTB < 33 weeks of gestation



CI, confidence interval.

Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018

Ref: Romero 2018

Romero 2017, is a systematic review and meta-analysis designed to assess the efficacy of vaginal progesterone in reducing the risk of PTB and adverse perinatal outcomes in asymptomatic women with a multiple pregnancy. The design of the analysis, and outcome measures considered are similar

6 individual RCT, met the inclusion criteria, with 159 women receiving vaginal progesterone and 144 placebo or no treatment.

PTB <33 weeks gestation (31.4% vs 43.1%; RR, 0.69 (95% CI, 0.51–0.93); P=0.01; I2=0%; six studies, 303 women; moderate-quality evidence) compared with those allocated to placebo/no treatment. In addition, PTB <35 weeks gestation (RR, 0.83 (95% CI, 0.69–0.99); moderate-quality evidence), < 34weeks gestation (RR, 0.71 (95% CI, 0.56–0.91); moderate-quality evidence), <32 weeks gestation (RR, 0.51 (95% CI, 0.34–0.77); moderate-quality evidence), <30 weeks gestation (RR, 0.47 (95% CI, 0.25–0.86); moderate-quality evidence), and spontaneous PTB at <33weeks gestation (RR, 0.67 (95% CI, 0.48–0.93); moderate-quality evidence) and <34 weeks gestation (RR, 0.71 (95% CI, 0.54–0.93); moderate-quality evidence). The number needed to treat to prevent one case of PTB occurring at <30 to <35 gestational weeks PTB

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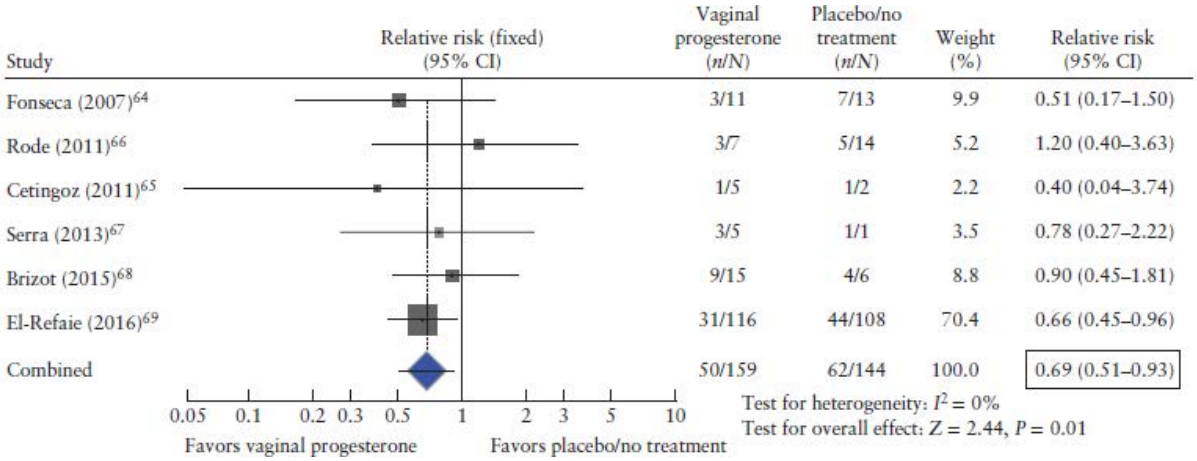
<37 weeks (moderate-quality evidence), <36 weeks (moderate-quality evidence) and <28 weeks (low-quality evidence) gestation.

The meta-analysis by Romero 2017 included three studies using vaginal progesterone 200 mg/day (capsule, pessary or ovule), one using vaginal progesterone pessaries 100 mg/day, one using vaginal progesterone pessaries 400 mg/day with the remaining study using vaginal progesterone suppositories 200 or 400 mg/day.

While the statistical robustness of the observation is uncertain due to low patient numbers in the 100 mg group, no difference in the relative risk of preterm births compared to placebo was seen for 100, 200 or 400 mg progesterone dosages (interaction test for subgroup differences p=0.4).

Table 2 - Forest plot of the effect of vaginal progesterone on the risk of PTB <33 weeks gestation



Ref: Romero 2017

Dodd 2013, is a systematic review and meta-analysis of randomised controlled studies, in which progesterone was administered for the prevention of PTB in singleton and multiple pregnancies either by intramuscular route using 17-hydroxy progesterone caproate (17-OHPC), or vaginal route using natural progesterone. Of the 36 studies included in the review, 30 trials, including 7561 women and 10,114 infants were included in the meta-analysis. All trials compared either vaginal or intramuscular progesterone with placebo or no treatment; with one study conducting a three-arm trial comparing two different doses of progesterone with placebo.

In a planned subgroup analysis of women with a short cervix and singleton pregnancy there was a statistically significant reduction in the risk of PTB < 34 weeks (RR 0.64; 95%: CI 0.45-0.90) and < 28 weeks gestation (RR 0.59; 95% CI: 0.37-0.93) with progesterone (any type) compared with placebo.

A planned subgroup analysis of women with a previous history of spontaneous PTB demonstrated a significant reduction in PTB < 37 weeks gestation with progesterone (any type) compared to placebo (RR 0.55; 95% CI: 0.42-0.74). There was a statistically significant reduction in perinatal mortality overall (RR 0.50; 95% CI: 0.33-0.75), and for PTB < 34 weeks gestation (RR 0.31; 95% CI: 0.14-0.69) with progesterone compared with placebo.

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There were no statistically significant differences identified for the outcomes developmental delay, intellectual impairment, motor impairment, visual impairment, hearing impairment, cerebral palsy, learning difficulties, height less than fifth centile, weight less than the fifth centile, infant weight at six, 12 and 24 months' follow up, infant length (cm) at six, 12 and 24 months' follow-up, and infant head circumference (cm) at six, 12 and 24 months follow-up.

The Dodd 2013 meta-analysis performed subgroup analysis by total weekly cumulative dose of progesterone (less than 500 mg versus greater than 500mg) and found no differential effect for prenatal death, PTB < 37 weeks, threatened preterm labour, caesarean section, antenatal steroids, need for tocolysis, respiratory distress syndrome, haemorrhage grades III or IV, necrotising enterocolitis, fetal death or neonatal death.

Dodd 2017, is a systematic review and meta-analysis of randomised controlled studies in women with a multiple pregnancy. The analysis found that for the primary outcome measure of PTB less than 34 weeks, women who received vaginal progesterone and those who did not had a similar risk of PTB before 34 weeks gestation (average RR 0.83, 95% CI 0.63 to 1.09; women = 1727; studies = 6; I2 = 46%; low-quality evidence). For the secondary maternal outcome measures, there were no clear differences between groups in any of the outcomes apart from women who received vaginal progesterone having fewer caesarean sections compared to the placebo group, although the difference between groups was not large (7%) (RR 0.93, 95% CI 0.88 to 0.98; women = 2143; studies = 6; I2 = 0%). However, many of the comparisons show a trend favouring progesterone treatment, with the upper limit of the CI approaching 1 in several analyses.

In terms of the secondary infant outcomes, there were no significant differences observed between groups for any of the infant outcomes apart from mechanical ventilation, which was needed by fewer infants whose mothers had received the vaginal progesterone (RR 0.61, 95% CI 0.48 to 0.77; infants = 3134; studies = 5). It is noteworthy however to observe that the incidence of birthweight less than 2500 g (RR 0.95, 95% CI 0.88 to 1.03; infants = 3079; studies = 4; I2 = 49%, moderate-quality evidence) and the relative risk of admission to neonatal intensive care unit (RR 0.93, 95%CI 0.87 to 1.00; infants = 4052; studies = 5; I2 = 25%), just failed to reach significance.

Jarde 2017 conducted a systematic review and meta-analysis of randomised controlled studies, in which progesterone was administered intravaginally (natural progesterone), orally (natural progesterone) or intramuscularly (17-OHPC) for the prevention of PTB in singleton pregnancies, and a similar metanalysis published in the same year that looked at prevention of PTB in multiple pregnancies.

Of the studies included, nine administered progesterone vaginally, with two using the 90 mg dose, four a 100 mg dose and three a 200 mg dose. Cerclage was studied in 12 studies and the cervical pessary in three studies. The three studies using the cervical pessary all used the Arabin type. In addition, one study compared 17-OHPC with cerclage and three studies compared natural progesterone with 17-OHPC.

Jarde 2017b found that in the 9,425 women included in the analyses, that progesterone (of any type) significantly reduced the odds of both PTB < 34 weeks (OR 0.44; 95% credible interval (CrI) 0.22–0.79) and < 37 weeks gestation (OR 0.58; 95% CrI 0.41–0.79), in singleton pregnancies compared with control. When progesterone was studied according to type of progesterone (either natural progesterone [per vagina or oral] or intramuscular 17-OHPC), only natural progesterone significantly reduced PTB < 34 weeks (OR 0.38; 95% CrI 0.19–0.69; NNT 8; low quality). Both natural

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progesterone and 17-OHPC significantly reduced PTB < 37 weeks (natural progesterone, OR 0.54; 95% CrI 0.36–0.76; NNT 8; moderate quality; 17-OHPC, OR 0.65; 95% CrI 0.42–0.96; NNT 11; moderate quality). There were no statistically significant subgroup differences between natural progesterone and 17-OHPC for either PTB < 34 weeks (P = 0.25) or <37 weeks (P = 0.48).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Progesterone is rapidly absorbed following vaginal administration. The time to peak plasma level varies depending on the individual and the dose administered. In general, peak plasma levels are reached within 3-8 hours with a decrease in levels over 24 hours.

Distribution

Progesterone is extensively protein bound (96-99%), principally to serum albumin and corticosteroid binding globulin.

Metabolism

Progesterone is extensively metabolized (conjugated) by the liver, to largely pregnanediols and pregnanolones. Orally taken progesterone has a short half-life and is rapidly cleared from the peripheral circulation because of this first past metabolism effect. However prolonged serum levels result from vaginal or rectal administration because absorption and action occur before biotransformation of it by the liver.

Excretion

Progesterone is primarily excreted renally (50 to 60%) as pregnanediol or the pregnanediol conjugate with minimal (10%) biliary and faecal excretion.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Progesterone did not induce chromosomal aberrations or sister chromatid exchanges in cultured human cells nor chromosomal aberrations or DNA strand breaks in rodent cells. Progesterone did not induce dominant lethal mutations in mice or chromosomal aberrations in the bone marrow of rats although studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg.

Weak clastogenic activity was found for progesterone in the rat hepatocyte micronucleus test after treatment with a high oral dose (100 mg/kg). Studies on transformation of rodent cells were inconclusive. Variable results were obtained in the mouse lymphoma tk assay. Progesterone was not mutagenic to bacteria.

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Carcinogenicity

Animal studies showed that progesterone was able to induce and/or promote the formation of mammary, uterine, ovarian, endometrial, cervical and vaginal tumours. The clinical relevance of these findings in animals remains unclear.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Other plastic laminate/Al blisters in a unit carton containing 5 (samples), 15 or 30 pessaries (not all pack sizes may be marketed).

15 individually wrapped pessaries in a glass jar (not currently marketed).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemical Name: Pregn-4-ene-3,20-dione

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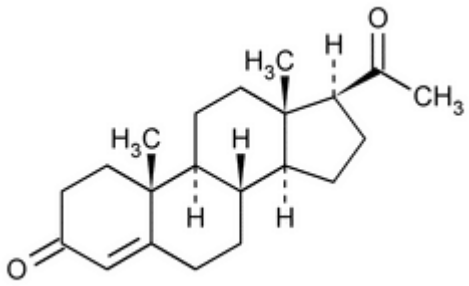

Molecular Formula: $C_{21}H_{30}O_2$

Molecular weight: 314.5

CAS number

57-83-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4: Prescription Only Medicine

8 SPONSOR

Orion Laboratories Pty Ltd T/A Perrigo Australia

25 – 29 Delawney Street

Balcatta

Western Australia

6021

Phone: 1800 805 546

9 DATE OF FIRST APPROVAL

December 2003

10 DATE OF REVISION

12 November 2019

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Updated to new PI format and editorial formatting changes for improved readability
4.1	Updated to reflect new indication
4.2	Updated to make editorial changes and include dosage for new indication.
	Additional text relating to use in pregnancy and lactation added
	Clinical trials information relating to the use of Oripro in PTB added
	Addition of blister material