

Attachment 1: Product information for AusPAR - Utrogestan 200 - progesterone - Besins Healthcare Australia Pty Ltd - PM-2020-06063-1-5 Final 24 November 2022. 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 It may have been superseded.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/products/australian-register-therapeutic-goods-artg/product-information-one>>

UTROGESTAN 200, soft capsule
PRODUCT INFORMATION

AUSTRALIAN PRODUCT INFORMATION

UTROGESTAN 200 (PROGESTERONE) SOFT CAPSULE (For Vaginal Use)

1. NAME OF THE MEDICINE

Progesterone

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Utrogestan contains the active ingredient: Progesterone (micronised) 200 mg.

Excipient with known effect: Soyabean lecithin .

For the full list of excipients, see section 6.1 List of Excipients

3. PHARMACEUTICAL FORM

Utrogestan 200 soft capsule is an ovoid, slightly yellow, soft capsule, containing a whitish oily suspension.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Utrogestan 200, soft capsules are indicated for:

Luteal phase support

- Luteal Support of Assisted Reproductive Technology (ART) cycles

Support during pregnancy

- Prevention of preterm birth in women with singleton pregnancy who have a short cervix (midtrimester sonographic cervix ≤ 25 mm) and/or a history of spontaneous preterm birth.
- Treatment of unexplained threatened miscarriage in women with bleeding in the current pregnancy and a history of at least three or more previous miscarriages.

Use in women with less than three miscarriages may be warranted in those with reduced chances of future pregnancy such as those undergoing IVF treatment with limited viable egg and/or embryo availability or advanced fertility age. However, the benefit of treatment in clinical trials was limited to women with three or more miscarriages. (See Section 5 Pharmacological properties; Clinical trials; Threatened Unexplained Miscarriage)

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4.2 DOSE AND METHOD OF ADMINISTRATION

Adults:

Luteal Phase Support (LPS)

The recommended dosage is 600 mg/day, in three divided doses, from the day of embryo transfer until at least the 7th week of pregnancy and not later than the 12th week of pregnancy.

Prevention of Preterm Birth (PTB)

The usual dose is 200 mg/day, recommended at bedtime. 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.

Threatened Miscarriage

The usual dose is 400 mg twice a day (morning and night). Treatment should be initiated at the first sign of vaginal bleeding during the first trimester of pregnancy (see Section 4.4 Special Warnings and Precautions for Use) and should continue to at least the 16th week of gestation.

Children: Not applicable.

Elderly: Not applicable

Method of Administration: Vaginal. Each capsule of Utrogestan must be inserted deep into the vagina.

The average dosage is 200 to 800 mg of progesterone per day to be introduced deep into the vagina. This may be increased, depending on the patient's response.

- In **partial luteal insufficiency** (dysovation): treatment should be given for 10 days per cycle, usually from **days 17 to 26** of the cycle, at a dosage of 200 mg of progesterone daily.
- In **sterility oocyte donation program**: the recommended dosage of progesterone is 100 mg on day 13 and 14 of the transfer cycle, followed by 100 mg of progesterone in the morning and evening, from days 15 to 25 of the cycle. From day 26, the dose should be increased - in early pregnancy - weekly, from 100 mg of progesterone per day up to a maximum of 600 mg of progesterone per day, as three divided doses. This dosage should be continued until day 60.
- In **luteal phase supplementation during ART (IVF)**, treatment should be started latest from the evening of the transfer, as 600 mg of progesterone in three divided doses, morning, midday and evening.
- In **the prevention of premature birth** the dosage is 200 mg daily in the evening at bedtime. 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.
- In **the treatment of unexplained threatened miscarriage**, the usual dose is 400 mg twice a day (morning and night). Treatment should be initiated at the first sign of vaginal bleeding during the first trimester of pregnancy and should continue to at least the 16th week of gestation.

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4.3 CONTRAINDICATION

Utrogestan should not be used in individuals with any of the following conditions:

- Known allergy or hypersensitivity to progesterone or to any of the excipients.
- Severe hepatic dysfunction.
- Undiagnosed vaginal bleeding.
- Known missed abortion or ectopic pregnancy.
- Mammary or genital tract carcinoma.
- Thromboembolic or thrombophlebitis disorders.
- Cerebral haemorrhage.
- Porphyria.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

During pregnancy, Utrogestan should be used for the recommended timeframes for each indicated use (see Section 4.2 Dose and Administration). Utrogestan should only be used by the vaginal route. Cases of cytolytic liver damage and cases of gravidic cholestasis were exceptionally reported during the administration of micronised progesterone during the 2nd and 3rd trimesters of pregnancy.

Utrogestan is not suitable for use as a contraceptive.

Women should insert each capsule deep into the vagina.

- If uterine bleeding is present, do not prescribe before establishing a cause, particularly with endometrial investigations.
- Patients must be monitored closely if they have a past history of venous thrombosis.

Treatment should be discontinued upon diagnosis of a missed abortion.

Utrogestan should be used cautiously in patients with conditions that might be aggravated by fluid retention (e.g. hypertension, cardiac disease, renal disease, epilepsy, migraine, asthma); in patients with a history of depression, diabetes, mild to moderate hepatic dysfunction, migraine or photosensitivity and in breast-feeding mothers.

There is limited evidence that supplementation with vaginal progesterone reduces the risk of preterm birth in women with twin/multiple pregnancy who have short cervix (midtrimester sonographic cervix \leq 25 mm) and/or a history of spontaneous preterm birth.

There is insufficient evidence to recommend the use of progesterone in women with preterm labour or 'other' risk factors for preterm birth.

Other known causes of threatened or recurrent miscarriage should be ruled out before initiating treatment in women with threatened or recurrent miscarriage.

Utrogestan contains soya lecithin which may cause hypersensitivity reactions (urticaria and anaphylactic shock).

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Use in the Elderly

No data available.

Paediatric Use

There is no experience in children as there is no relevant indication for use of Utrogestan in children. Utrogestan has not been evaluated in adolescents with child-bearing potential.

Effect on laboratory tests

Utrogestan may affect the results of laboratory tests of hepatic and/or endocrine functions.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Progesterone is metabolised primarily by the liver. Caution should be taken with drugs that are P450 enzyme inducers and inhibitors.

Metabolism of Utrogestan is accelerated by rifamycin an antibacterial agent.

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole ($IC_{50} < 0.1 \mu M$), a known inhibitor of cytochrome P450 3A4. These data therefore suggest that ketoconazole may increase the bioavailability of progesterone. The clinical relevance of the *in vitro* findings is unknown.

Combination with other medicinal products may decrease progesterone metabolism which may alter its effect.

This applies to:

- potent enzyme inducers such as barbiturates, antiepileptics (phenytoin), rifampicin, phenylbutazone, spironolactone and griseofulvin. These medicinal products increase hepatic metabolism.
- some antibiotics (ampicillins, tetracyclines): changes in the intestinal flora leading to a change in the steroid enterohepatic cycle.

Utrogestan may interfere with the effects of bromocriptine and may raise the plasma concentration of cyclosporin.

As these interactions may vary between people, the clinical results are not necessarily predictable.

Progestogens, but not natural progesterone may impair glucose tolerance and, because of this, increase requirements for insulin or other antidiabetic agents in diabetic patients.

The bioavailability of progesterone may be reduced by smoking and increased by alcohol abuse.

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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 (Category A)

Progesterone crosses the placenta. No association has been found between the maternal use of progesterone in early pregnancy and fetal malformations. Data on the risk of fetal effects with exposure in later stages of pregnancy are limited. Male and female genital abnormalities (hypospadias and virilisation) have been observed in fetuses of animals treated with progesterone during gestation.

Use in Lactation

Detectable amounts of progesterone enter the breast milk. Therefore, Utrogestan should not be used during lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Cases of drowsiness and dizzy sensations have been reported for the oral form.

Drivers and machine operators in particular, are alerted to the risks of drowsiness and/or dizziness associated with oral use of this medicinal product. These problems can be avoided by taking the capsules at bedtime.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECT)

No major local intolerance issues have been reported during the different clinical trials even if some burning, pruritus or fatty discharge have been observed and reported in the literature; incidences were extremely low.

No systemic side effects, in particular somnolence or dizziness (observed with the oral form), have been reported during clinical studies at the recommended dosages.

No significant safety concerns for the mother or for the foetus were identified with vaginally administered Utrogestan during pregnancy. Maternal outcomes were unaffected. Treatment-related adverse effects were generally mild and transient, and the incidence was no greater than those reported for placebo or no treatment. The adverse effect profile was consistent with the established safety profile of Utrogestan for ART.

The beneficial effects of progesterone to prevent preterm birth in women with a short cervix and/or a history of preterm birth is expected to improve neonatal outcomes. There is no evidence that fetal progesterone exposure in the 2nd and 3rd trimester adversely affects childhood neurodevelopmental outcomes.

Consistent with the well-established safety profile of vaginally administered progesterone for support in the luteal phase and for support during pregnancy for women at risk of preterm birth, progesterone for the prevention of miscarriage does not appear to increase the risk of congenital malformations. Incidence of adverse neonatal outcomes and serious maternal adverse events were low with no differences observed between progesterone and placebo groups during the 1st and 2nd

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trimester. The adverse effect profile remains unchanged regardless of the timing or duration of treatment during pregnancy with beneficial effects of progesterone expected to increase the number of live births in women with threatened miscarriage or a history of recurrent miscarriage.

Table 1 – Adverse events from PROMISE trial

Category	Progesterone (N=404), n (%)	Placebo (N= 432), n (%)
Allergy	2 (0.5)	0 (0.0)
Dermatological	1 (0.2)	3 (0.7)
Gastrointestinal	20 (5.0)	14 (3.2)
Haematological	0 (0.0)	1 (0.2)
Neurological	7 (1.7)	4 (0.9)
Urological	3 (0.7)	4 (0.9)
Miscellaneous	8 (2.0)	4 (0.9)

Table 2 – Adverse events from PRISM trial

Serious adverse event	Progesterone, n/N (%)	Placebo, n/N (%)	RR, 95% CI; p-value
Total number of participants experiencing a SAE (either maternal or neonatal)	105/2025 (5)	98/2013 (5)	1.07, 0.81 to 0.39; p=0.65
Total number of SAEs	133/2025 (7)	126/2013 (6)	
Maternal	83/2025 (4)	83/2013 (4)	
Neonatal	50/2025 (2)	43/2013 (2)	

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Category	Progesterone, n	Placebo, n
Maternal		
Bone and joint injuries	2	0
Cardiac disorders	1	2
Congenital, familial and genetic disorders	3	0
Endocrine disorders	1	2
Eye disorders	1	0
Gastrointestinal disorders	0	1
General disorders and administration site conditions	1	6
Infections and infestations	2	4
Metabolism and nutrition disorders	0	1
Nervous system disorders	1	2
Pregnancy, puerperium and perinatal conditions	46	46
Renal and urinary disorders	3	2
Reproductive system and breast disorders	11	9
Respiratory, thoracic and mediastinal disorders	10	7
Skin and subcutaneous tissue	0	1
Vascular disorders	1	0
Total	83	83
Neonatal		
Congenital, familial and genetic disorders	23	22
Gastrointestinal disorders	0	1
General disorders and administration site conditions	1	3
Metabolism and nutrition disorders	2	1
Nervous system disorders	0	1
Pregnancy, puerperium and perinatal conditions	17	11
Renal and urinary disorders	1	3
Reproductive system and breast disorders	1	0
Respiratory, thoracic and mediastinal disorders	3	1
Skin and subcutaneous tissue	1	0
Vascular disorders	1	0
Total	50	43

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Post-Marketing Experience

The information given below is based on extensive post marketing experience from vaginal administration of progesterone.

Adverse effects have been ranked under headings of frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); frequency not known (cannot be estimated from the available data).

Table 3: Post-marketing experience of vaginal administered progesterone

System organ class	Very Rare ($< 1/10,000$)	Frequency Not Known (cannot be estimated from the available data)
Immune system disorders	Anaphylactic reactions	
Reproductive system and breast disorders		Vaginal haemorrhage Vaginal discharge
Skin and subcutaneous tissue disorders	Application site pruritis, Burning sensation	
General Disorders		Drug intolerance

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 of overdose (more frequent with the oral route of administration) may include somnolence, dizziness, euphoria or dysmenorrhoea. Treatment is observation and, if necessary, symptomatic and supportive measures should be provided.

Although no overdose has been reported to date for the vaginal form, the adverse effects described above are usually signs of overdose. These disappear without treatment when the dosage is reduced.

In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26) for advice.

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5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Progesterone is a naturally occurring steroid hormone that is secreted by the ovary, placenta and adrenal gland. It acts on the endometrium by converting the proliferating phase to the secretory phase. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo, and once an embryo is implanted, progesterone acts to maintain the pregnancy. As well as gestagenic actions, progesterone also has anti-estrogenic, slightly anti-androgenic and anti-aldosterone effects.

Clinical Trials

Luteal phase support

Two company-sponsored studies have been conducted to investigate efficacy of Utrogestan for luteal phase support.

1. Study Kleinstein 2002 was an open, multicentre, comparative controlled, randomised, parallel group phase III trial that compared the efficacy and safety of vaginal Utrogestan 200 mg three times daily and vaginal 1.125 g Crinone 8% gel twice daily, for up to 12 weeks, in providing luteal phase support to women undergoing IVF [Kleinstein 2005].

The primary end point was the ongoing pregnancy rate at the end of the 12th week of gestation. The implantation and abortion rates and the rate of withdrawals, overall or at the respective visits, were considered as secondary study end points.

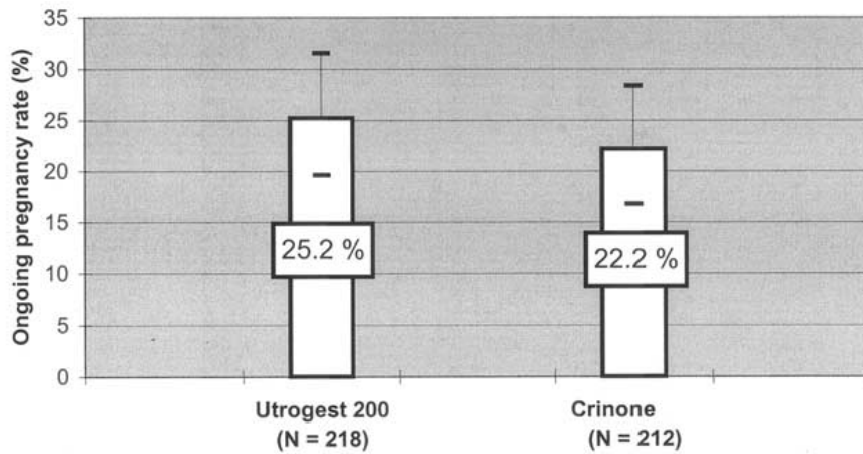
Fifty-five (55) patients in the Utrogestan group and forty-seven (47) patients in the progesterone gel group completed the study. These were all women with ongoing pregnancies at or beyond the 12th week of gestation. Ongoing pregnancy rates were 25.2% (95% confidence interval [CI]: 19.6%–31.5%) for the Utrogestan group and 22.2% (95% CI: 16.8%–28.4%) for the progesterone gel group (Figure 1). The odds ratio (OR) (calculated on the per-protocol population) for an intact pregnancy at the end of 12th week of gestation was 1.185 (90% CI: 0.733–1.833) when the Utrogestan group was compared with the progesterone gel group. According to the pre-specified criteria, the pregnancy rate in the Utrogestan group was demonstrated to be non-inferior to that in the progesterone gel group (lower limit of the 90% confidence interval >-0.1).

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Figure 1: Point estimate and 95% confidence limits of pregnancy rates in women regularly completing the study with an ongoing pregnancy at or later than 12 weeks gestation in the per protocol population



The implantation and abortion rates were also considered to be equivalent between the Utrogestan 200 group and Crinone 8% group (Table 4)

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Table 4: Summary of implantation and abortion outcomes in women receiving Utrogestan 200 mg or Crinone 8%

Variable	Utrogestan® 200	Crinone® 8%
No. of transfers	218	212
No. of embryos transferred	489	481
No. of implantations (% per transferred embryos)	71 (14.7)	57 (11.9)
No. of clinical pregnancies (% per transfer)	55 (25.2)	47 (22.2)
No. of abortions / missed abortions (% of clinical pregnancies)	10 (18.2)	9 (19.1)

More than 90% of women rated overall tolerability of the study drugs as “very good” or “good”. Similarly, acceptance of either treatment was positively assessed in > 90% of women by the physicians. Nevertheless, both items indicated an overall significant difference (P<0.0001) of the effect index, as calculated from rank sums, in favour of Utrogestan.

These efficacy findings are consistent with the company-sponsored bioavailability study showing that the vaginal bioavailability of micronised progesterone following administration of a Utrogestan 200 mg capsule and Crinone 8% gel (90 mg progesterone) in young healthy women was therapeutically at least equivalent to that of the vaginal gel [Kleinstein 2002].

The role of progesterone for luteal phase support in stimulated IVF cycles is well established and supported by several recent meta-analyses [Nosarka 2005; Polyzos 2010; Pritts & Atwood 2002; van der Linden 2012, van der Linden 2015, Zarutskie & Phillips 2009, Lin 2012]. However, several meta-analyses included data from RCTs with an unclear or high risk of bias. In general, findings from the meta-analyses showed no significant differences in clinical pregnancy rate between the different formulations of vaginal progesterone (gel, capsule, inserts, pessaries)[Polyzos 2010, Zarutskie & Phillips 2009] but the relative benefit of the various routes of administration (oral, IM, vaginal) is unclear. Despite this, the vaginal route is often preferred because of better patient comfort [Vaisbuch 2014].

The use of progesterone for luteal phase support was recently reviewed in detail by the UK National Institute for Care Excellence (NICE) in 2013, to provide guidelines on treatment options for luteal phase support in fertility treatments. This was a significant assessment, which involved detailed review of all existing published evidence on the use of progesterone for luteal phase support. Overall, the evidence from the current published clinical studies was judged to be of low to very low quality; largely due to poor reporting on the details of the studies and lack of reported power calculations. Studies may have been underpowered for many of the reported outcomes, as shown by the wide confidence intervals around power estimates. However, it is clear that much of the evidence is over 20 years old and new research is unlikely to be conducted because of the well accepted role of luteal phase support in IVF treatment.

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Notwithstanding any weaknesses in the data, the NICE 2013 guidelines, which are consistent with the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) guidelines, recommend the following:

- There is evidence that luteal phase support with progesterone is associated with significantly more live full-term singleton births and clinical pregnancies than placebo or no support. Progesterone is therefore the drug of choice recommended for luteal phase support.
- There was no significant difference in the number of clinical pregnancies and live full-term singleton births when comparing the different types of drugs used for luteal phase support. However, the evidence showed that the use of hCG for luteal phase support was associated with an increased risk of ovarian hyperstimulation syndrome compared with the use of progesterone. Therefore, hCG is not recommended for luteal phase support.
- In terms of duration of treatment, luteal phase support should be offered for up to 8 weeks after embryo transfer and patients should be informed that there is no evidence for continuing luteal phase support after this time.

2. Study Salat-Baroux 1988 was a one-arm, prospective study that evaluated endometrial morphology and pregnancy outcomes following the administration of Utrogestan and oestradiol in women without ovarian function participating in an oocyte donation program.

The aim of this clinical study was to demonstrate adequate endometrial maturation in women lacking ovaries after the vaginal administration of progesterone and pregnancy after the transfer of frozen embryos, thawed in the context of oocyte donation.

One capsule of Utrogestan (100 mg natural micronised progesterone) was inserted into the vagina by the subject on Days 13 and 14 in the evening. On Days 15 to 25 an additional capsule was inserted in the morning. The dose was then regularly increased to 300, 400, 500 and 600 mg/day maximum until Day 60.

The primary outcome measure was the effectiveness of vaginal progesterone as assessed by plasma progesterone concentrations (Days 13, 15 and 21) and endometrial histology.

Endometrial biopsies on Days 21 or 22 of a substitution cycle were found to be, on average, typical of endometria on Days 21 \pm 2 (average \pm SD) of a normal 28-day menstrual cycle in 18 of the 22 women. In the other 4 women, 3 cases of moderate hypotrophy and 1 case of severe hypotrophy were observed.

There were 11 pregnancies out of 32 transfers (34%).

In conclusion, findings from this clinical trial demonstrated that the vaginal administration of natural micronised progesterone enables an adequate maturation of the endometrium in women without functioning ovaries.

These findings are supported by a meta-analysis of 9 RCTs (1620 women) [van der Linden M 2012] of varying quality comparing vaginal versus IM progesterone in women undergoing ART. The meta-analysis showed no differences for ongoing and clinical pregnancy or live birth rate between vaginal progesterone (gel or capsule) and IM progesterone as luteal support for women undergoing ART. Although a meta-analysis of data from 22 RCTs (3451 women) of moderate risk of bias

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found insufficient evidence to recommend any one particular protocol for endometrial preparation over another with regard to pregnancy rates after embryo transfers, there was evidence of a lower pregnancy rate when progesterone supplementation is commenced before oocyte retrieval in oocyte donation cycles.

The role for progesterone as support during the luteal phase of IUI cycles is not well established. Although progesterone and hCG are both used for luteal phase support, progesterone may be the preferred over hCG because of the potential for ovarian hyperstimulation syndrome with hCG [van der Linden 2011]. No company-sponsored studies were conducted to support this indication. Two meta-analyses [Hill 2013; Miralpeix 2014] including the same 5 open-label RCTs of mixed quality, evaluated vaginal progesterone as luteal support in the following formulations: gel (Crinone 8% 90 mg/day, 2 RCTs), capsules (Utrogestan 600 mg/day, 1 RCT), or suppositories (Cyclogest 400 mg/day, 2 RCTs). Findings from these meta-analyses showed that vaginal progesterone increased the likelihood of clinical pregnancy and live birth per cycle and may be of benefit in women undergoing ovulation induction with gonadotropins, but not clomiphene citrate, during IUI.

Moreover recently, a retrospective evaluation of the luteal phase of 579 IUI cycles from 2010 to 2013 was conducted to determine the effect of luteal phase support on clinical pregnancy and live birth rates after ovulation induction and IUI [Oktem 2014]. Ovarian stimulation was performed with gonadotropins, and recombinant hCG was used for ovulation triggering. The use of vaginal progesterone gel (Crinone) or micronised progesterone vaginal capsules (Besins progesterone capsules) were found to significantly improve clinical pregnancy rates.

Support during pregnancy

Prevention of Pre-term birth

Study UTRO-200-PTD (MISTERI) 2014 was an open-label, multicentre, one-arm phase III study that evaluated whether the prophylactic use of 200 mg vaginal progesterone daily in weeks 19-34 of pregnancy reduces the rate of preterm birth in women at high risk for preterm birth.

The primary objective of the study was to improve obstetric outcomes by prolonging pregnancy and thereby reducing the rate of preterm birth (birth prior to 34+0 weeks) with prophylactic use of 200 mg/day natural progesterone (Utrogestan) in weeks 19-34 of gestation in women at high risk for preterm birth compared to the population at risk of preterm birth.

All patients (N = 220) who enrolled in the study received 200 mg/day Utrogestan vaginally for 10 to 15 weeks, depending on the gestational age at enrolment. Treatment was started no earlier than week 19+0 and no later than week 24+0 of pregnancy and the maximum duration of treatment was 15 weeks (weeks 19 to 34 of gestation).

One hundred and ten (110) patients were grouped as:

- Patients with a shortened cervix (uterine cervix length of >10 and <25 mm at weeks 18-24 of gestation) and
- Patients with anamnestic risk factors (a prior preterm birth or premature rupture of membranes).

Patients with both risk factors were included in the shortened cervix group.

The investigators concluded that, according to the data generated in the study, the risk of preterm birth prior to 34 weeks was effectively reduced by treatment with vaginal Utrogestan 200 mg

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capsules in patients with preterm birth risk factors (cervical shortening and medical history of preterm birth and/or preterm premature rupture of membranes).

The company-sponsored study is supported by systematic reviews, meta-analyses and numerous investigator-sponsored studies similarly showing a significantly lower risk of preterm birth before 34 weeks gestation in women with a short cervix and/or a history of preterm birth.

Short Cervix and/or history of Preterm birth

Fonseca 2007 was a randomised, double-blind, placebo-controlled trial that examined the effects of vaginal progesterone for the prevention of preterm birth in women with a short cervix. In this study women were allocated to receive either Utrogestan 200 mg/day or placebo from 24 to 34 weeks gestation with the primary aim to measure the frequency of spontaneous preterm delivery at <34 weeks of gestation. Patients treated with Utrogestan had a lower rate of preterm delivery (<34 weeks) than those in the placebo group [19.2% (24/125) vs 34.4% (43/125)].

Norman 2016 [OPPTIMUM study] was a double-blind, placebo-controlled randomised clinical trial conducted in a heterogeneous group of women at risk of PTB to determine whether vaginal progesterone (200 mg daily from 22-24 weeks to 34 weeks of gestation) reduced the risk of preterm birth. The study also assessed whether progesterone prophylaxis affects neonatal and childhood outcomes.

Although the odds ratios (OR) was in the direction of benefit, administration of progesterone did not significantly alter the risk of obstetric outcomes (fetal death or birth <34 weeks; OR 0.86) or neonatal outcome (a composite of death, brain injury or bronchopulmonary dysplasia; OR 0.62) in this heterogeneous population of women at risk of PTB. Progesterone prophylaxis for preterm birth had no effect on childhood outcomes (at 2 years).

The OPPTIMUM trial reported a non-significant 38% reduction in the risk of neonatal death or serious neonatal morbidity, which is very similar to the 43% significant reduction in the risk of composite neonatal morbidity and mortality found in a previous Individual Patient Data (IPD) Meta-analysis by Romero (RR 0.59, 95% CI 0.38-0.91) (Romero 2012).

In a subgroup analysis of women with a short cervix ≤ 25 mm, the point estimates for neonatal composite effects in the OPPTIMUM study (OR 0.54; CI 0.25-1.16) was comparable to the RR of 0.57 in the IPD meta-analysis by Romero and colleagues (Romero 2012).

It is noteworthy that the OPPTIMUM trial was underpowered to detect a meaningful difference between vaginal progesterone and placebo in the subgroup of women with a CL ≤ 25 mm. Therefore, a new Individual Patient Data level meta-analysis including OPPTIMUM trial results, was mandatory to understand what the totality of evidence indicates, particularly within subgroups of interest and to address the effect of vaginal progesterone for the most powerful risk factor (short cervix), as suggested by the authors in the publication (Norman 2016).

A first aggregate meta-analysis, including the OPPTIMUM data, was published shortly after the release of the OPPTIMUM study data to quantify the efficacy of vaginal progesterone to improve perinatal morbidity and mortality in asymptomatic women with a singleton gestation and a midtrimester short cervix (Romero 2016). In 5 RCTs including 974 women, vaginal progesterone was associated with a 34% reduction in the risk of PTB ≤ 34 weeks or fetal death (RR 0.60, 95% CI, 0.52-0.83, $P=0.0005$). Composite neonatal morbidity and mortality was also significantly reduced

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in women treated with vaginal progesterone, along with a reduction in RDS, birth weight <1500 g and admission to NICU.

Following on from the 2016 aggregate meta-analysis, an in-depth individual participant data (IPD) meta-analyses, which included individual patient data from the OPPTIMUM trial, reported with Level I evidence that vaginal progesterone reduces the risk of PTB and improves perinatal outcomes in singleton gestation with a midtrimester short cervix (Romero 2018). Vaginal progesterone had no effect on childhood neurodevelopmental outcomes.

Several further meta-analyses on the use of progesterone in the prevention of preterm birth have been published, each of which further supports the use of vaginal progesterone in the prevention of preterm birth in pregnant women with a midtrimester short cervix with reductions in neonatal morbidity and mortality (Romero 2017; Romero 2012; Conde-Agudelo 2018; Jarde 2017a; Jarde 2017b; Schuit 2014; Dodd 2013; Velez Edwards 2013; Sotiriadis 2012; Likis 2012; Mckenzie 2006). Together these findings suggest that routine screening of women to detect short cervical length at the mid-trimester and prophylactic administration of progesterone to those found to have a short cervix is warranted.

Meta-analyses of randomised controlled trials have also demonstrated that daily vaginal progesterone, initiated at around 16 weeks' gestation, prevents PTB in women with a history of spontaneous PTB (Conde-Agudelo 2018; Saccone 2017; Jarde 2017a; Jarde 2017b; Oler 2017; Dodd 2013; Sotiriadis 2012; Likis 2012; Dodd 2005).

A 2013 Cochrane review assessed the benefits and harms of progesterone for the prevention of preterm birth in women with a history of preterm birth (Dodd 2013). The findings, all significantly in favour of progesterone, included a reduction in the risk of preterm birth at <34 and <37 weeks gestation and a significant increase in pregnancy prolongation, significant improvements in perinatal mortality, infant birthweight, use of assisted ventilation, necrotising enterocolitis, neonatal death and admission to NICU (Dodd 2013).

Treatment of Unexplained Threatened miscarriage

The PROMISE trial (Coomarasamy 2015) was designed to evaluate the effects of progesterone in the 1st trimester, not during the luteal phase, and because progesterone treatment was initiated only after urinary pregnancy test was confirmed, the study did not address whether progesterone supplementation would be more effective in reducing the risk of miscarriage if administered during luteal phase of the cycle, before confirmation of pregnancy.

Progesterone supplementation in early pregnancy has been attempted in two contexts: the first is to prevent miscarriages in asymptomatic women who have a history of recurrent miscarriages (as in the PROMISE trial) and the second was to rescue a pregnancy in women who have started to bleed during early pregnancy (Wahabi 2018). As no beneficial effect of progesterone in women with a history of unexplained recurrent miscarriages was found in PROMISE, the second scenario was evaluated in the PRISM trial, the largest randomised trial conducted evaluating progesterone in women with early pregnancy bleeding.

The intervention in the PRISM trial was Utrogestan 400 mg administered vaginally twice daily or placebo pessaries. The 800 mg daily dose, divided into 2 doses, is considered to be a clinically effective dose based on luteal phase support data. Progesterone therapy continued until 16 weeks'

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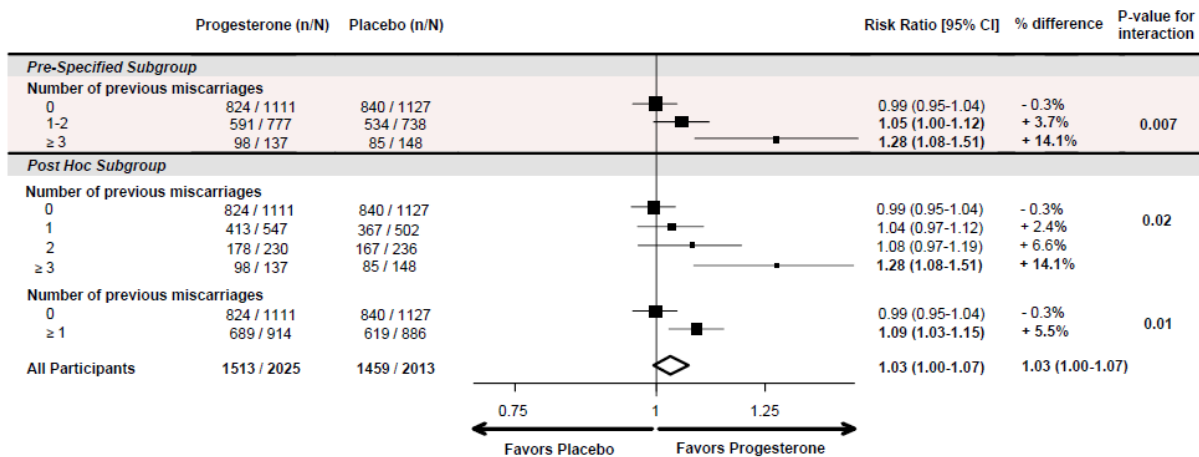
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gestation. At this critical luteoplacental juncture of pregnancy, placental progesterone is biologically more important than luteal progesterone.

The primary outcome of the PRISM trial was a live birth after at least 34 weeks gestation. Live births were greater in the progesterone group (75% in the progesterone group vs. 72% in the placebo group (RR, 1.03; 95% CI, 1.00-1.07, p=0.08)) and this primary outcome achieved borderline significance (Coomarasamy 2020a, HTA, Coomarasamy 2019, NEJM PRISM Trial). Progesterone resulted in an additional 2 live births per 100 women at ≥34 weeks of gestation compared with placebo (Coomarasamy 2020b, ACOG). Live birth rate after 24 weeks of gestation was 66% in the progesterone group compared with the 63.3% in the placebo group (relative rate, 1.04: 95% CI, 0.94-1.15: absolute risk difference, 2.5 percentage points: 95% CI, -4.0 to 9.0).

A subgroup effect by previous history of miscarriage was observed in pre-specified subgroup analysis. Analysis revealed a biological gradient, whereby women with 1 or 2 previous miscarriages gained some benefit and those with ≥3 previous miscarriages received a considerably significant benefit. In women with threatened miscarriage and a history of 1 or more miscarriage(s), the number needed to treat for 1 additional live birth is 20. In women with a history of 3 or more miscarriages, the number needed to treat is 8. The biological gradient of progesterone combined with the borderline significant live birth rate provides assurance of the positive effects of progesterone in women at high-risk of miscarriage.

FIGURE 2
PRISM trial data on live birth >34 weeks by the number of previous miscarriages



CI, confidence interval; PRISM, PRogesterone In Spontaneous Miscarriage.

Coomarasamy et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol 2020.

In summary, the dual risk factors of early pregnancy bleeding and a history of one or more previous miscarriage(s) identified high-risk women in whom progesterone may be of benefit. It is suggested that the information should be communicated to women at high risk of miscarriages to enable shared decision-making and consider offering to women with vaginal bleeding and a history of 1 or more previous miscarriage(s) a course of treatment with vaginal micronized progesterone 400 mg twice daily, started at the time of presentation with vaginal bleeding and continued to 16 completed weeks of gestation. (NICE 2021) In the United Kingdom, they estimated that implementing this treatment strategy would result in an additional 8450 live births per year and believed that a woman at high

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risk of having a miscarriage may not need absolute scientific certainty to choose to have this treatment (Coomarasamy 2020b, ACOG).

A Cochrane network meta-analysis including seven randomised trials involving 5682 confirmed that vaginal micronized progesterone may increase the live birth rate for women with a history of one or more previous miscarriages and early bleeding pregnancy (Devall 2021). For women with one or more previous miscarriages and early pregnancy bleeding, vaginal micronized progesterone increased the live birth rate compared to placebo (RR 1.08, 95% CI 1.02 to 1.15, high-certainty evidence). (Devall 2021).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, micronised progesterone is absorbed by the digestive tract. Pharmacokinetic studies conducted in healthy volunteers have shown that after oral administration of two 100 mg capsules (200mg), plasma progesterone levels increased to reach the C_{max} of 13.8ng/ml +/- 2.9ng/ml in 2.2 +/- 1.4 hours. The elimination half-life observed was 16.8 +/- 2.3 hours.

Although there were inter-individual variations, the individual pharmacokinetic characteristics were maintained over several months, indicating predictable responses to the drug.

Following vaginal administration, micronised progesterone is absorbed rapidly and achieves stable plasma levels in the range of 4-12 ng/ml, depending on the daily dose, with much less inter-subject variation than following oral administration.

Distribution

Following vaginal administration of micronised progesterone, relatively high concentrations of progesterone are found in the uterus and nearby tissues with correspondingly low systemic exposure. Progesterone enters both the lymph system and the blood vessels, as outlined for the uterine first-pass effect. Progesterone is approximately 96-99% bound to serum proteins, primarily to serum albumin (50-54%) and transcortin (corticosteroid binding globulin) (43-48%).

Metabolism

Progesterone is metabolised primarily by the liver. Following oral administration, the main plasma metabolites are 20α hydroxy- $\Delta 4\alpha$ -prenolone and 5α -dihydroprogesterone. Some progesterone metabolites are excreted in the bile and these may be deconjugated and further metabolised in the gut via reduction, dehydroxylation and epimerisation.

The main plasma and urinary metabolites are similar to those found during the physiological secretion of the corpus luteum.

Following vaginal administration, only low plasma levels of pregnanolone and 5α -dihydroprogesterone are detected, due to the lack of first-pass metabolism.

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Excretion

Urinary elimination is observed for 95% in the form of glycoconjugated metabolites, mainly 3 α , 5 β -pregnanediol (pregnandiol).

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 in vivo although in vivo 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 *in vitro* were inconclusive. Variable results were obtained in the mouse lymphoma tk assay. Progesterone was not mutagenic to bacteria.

Carcinogenicity

Progesterone has been shown to induce/promote the formation of ovarian, uterine, mammary, and genital tract tumours in animals. The clinical relevance of these findings is unknown. Literature data provides no indication of potential carcinogenicity in humans.

When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors and endometrial stromal sarcomas. In dogs, long-term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen.

The exposure to women remains always in the physiological range of progesterone and is regarded as hormone replacement therapy whatever the indication.

6. PHARMACEUTICAL PARTICULAR

6.1 LIST OF EXCIPIENTS

Sunflower oil
Lecithin
Gelatin
Glycerol
Titanium dioxide
Purified water

6.2 INCOMPATIBILITIES

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

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6.3 SHELF-LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.
Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

Utrogestan is supplied in a PVC/aluminium blisters packaged in an outer carton.

Utrogestan 200 is available in pack sizes of 7 (trade or starter pack), 14, 15, 21, 28, 30, 42, 45, 56, 84 or 90 capsules*.

*Not all pack sizes may be marketed.

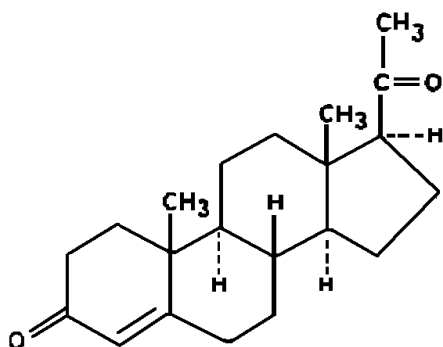
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

Progesterone is a white or almost white crystalline powder or colourless crystals, is practically insoluble in water, freely soluble in ethanol and sparingly soluble in acetone and in fatty oils.

Chemical structure



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

Molecular formula: C₂₁H₃₀O₂

MW: 314.5

CAS Number

57-83-0

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7. MEDICINE SCHEDULE (POSITION STANDARDS)

Schedule 4 - Prescription Only Medicine

8. SPONSOR

Besins Healthcare Australia Pty Ltd,
Level 16, Tower 2, Darling Park,
201 Sussex Street,
Sydney, NSW 2000

9. DATE OF FIRST APPROVAL

12 July 2016

10. DATE OF REVISION

22 February 2022

Summary table of changes

Section changed	Summary of new information
4.1, 4.2, 4.4, 4.8, 5.1 Clinical Trials	Changes as result of new indication