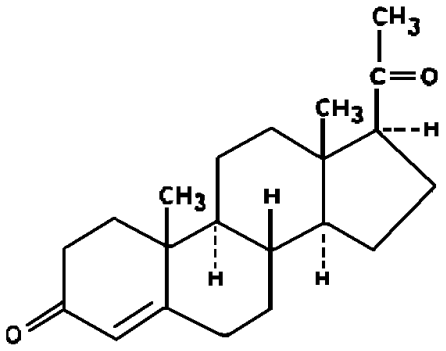
PRODUCT INFORMATION

UTROGESTAN 200 mg
(For Vaginal Use)

NAME OF THE MEDICINE

Progesterone (micronised) 200 mg, soft capsule

Progesterone



Chemical name: Pregn-4-ene-3,20-dione
Molecular formula: $C_{21}H_{30}O_2$.
MW: 314.5
CAS: 57-83-0.

DESCRIPTION
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.

The capsule contains the following active ingredient: Progesterone (micronised) 200 mg. It also contains sunflower oil, soya lecithin, gelatin, glycerol and titanium dioxide.

PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

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 Cmax 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-Δ4α-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.

Excretion
Urinary elimination is observed for 95% in the form of glycuroconjugated metabolites, mainly 3α, 5ß–pregnanediol (pregnandiol).

CLINICAL TRIALS

Luteal phase support

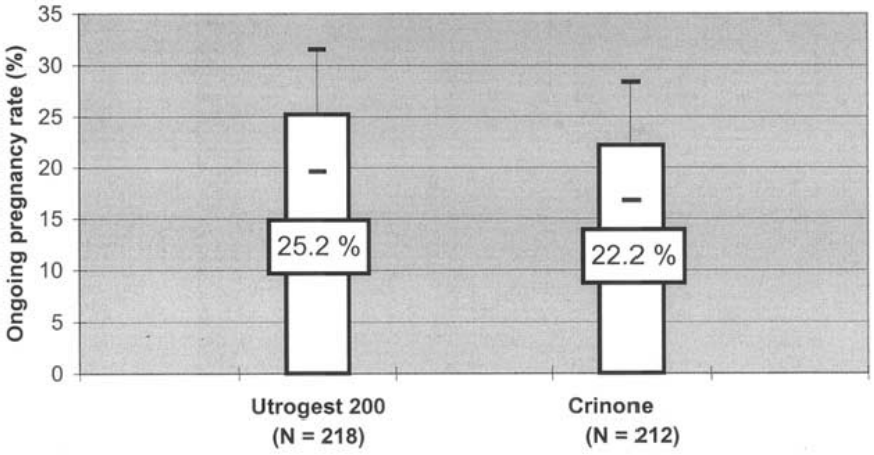
Two company-sponsored studies have been conducted to investigate efficacy of Utrogestan for luteal phase support.

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.

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).

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 1)

Table 1: 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< .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.

The role of progesterone for luteal phase support in stimulated IVF cycles is well established and supported by several recent meta-analyses[Nosarka S et al 2005;Polyzos N et al 2010;Pritts A , Atwood A 2002; van der Linden M 2012, Zarutskie P, Phillips J 2009, Lin K et al 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 N et al 2010, Zarutskie P, Phillips J 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 E et al 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. Also 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.

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 an 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 ± 2 (average ± 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 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[65]. No company-sponsored studies were conducted to support this indication. Two meta-analyses[68, 69], 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 M et al 20104]. 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.

INDICATIONS

Utrogestan 200 mg, soft capsules are indicated for:

Luteal phase support

- Luteal Support of Assisted Reproductive Technology (ART) cycles

CONTRAINDICATIONS

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.

PRECAUTIONS

During pregnancy, Utrogestan should only be used during the first three months and only by the vaginal route. Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.

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.

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.

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

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.

Paeadiatric Use
There is no experience in children as there is no relevant indication for use of Utrogestan in children

Use in the Elderly
Not applicable.

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.

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.

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

INTERACTIONS WITH OTHER MEDICINES
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 µM), 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.

ADVERSE EFFECTS

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.

DOSAGE AND ADMINISTRATION

Adults:
In the Luteal Phase Support (LPS) in Controlled Ovarian cycles (COS):

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.

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 600 mg of progesterone per day to be introduced deep into the vagina, possibly using an applicator. This may be increased, depending on the patient's response.

- In **partial luteal insufficiency** (dysovulation,): 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 **threatened miscarriage or to prevent repeated miscarriage due to luteal insufficiency**, the average dosage is 200 mg to 400 mg of progesterone daily, as two divided doses until week 12 of pregnancy.

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.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Utrogestan 200 mg, soft capsule is an ovoid, slightly yellow, soft capsule, containing a whitish oily suspension.
Utrogestan is supplied in a PVC/aluminium blisters packaged in an outer carton.

Utrogestan 200 mg, soft capsule is available in pack sizes of 7, 14, 15, 21, 28, 30, 42, 45, 56, 84 or 90 capsules*.

*Not all pack sizes may be marketed.

Storage

Store below 30^{o}C.
Do not refrigerate.
Store in the original container.

NAME AND ADDRESS OF THE SPONSOR

Besins Healthcare Australia Pty Ltd,
Level 23 Governor Macquarie Tower
1 Farrer Place,
Sydney NSW 2000

AUSTR : 232824

POSION SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

12 July 2016