UTROGESTAN 200mg capsules

Progesterone

1 PRODUCT NAME

UTROGESTAN 200MG CAPSULES

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Soft, ovoid, slightly yellow capsule containing a whitish oily suspension of 200 mg progesterone (micronised).

Excipient(s) with known effect: Soya lecithin (fully refined), sulfites (from gelatin)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsules, soft

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

UTROGESTAN 200 mg capsule is indicated in adults, *via* the oral or vaginal route, for:

Oral Route

- ***Hormone replacement therapy***

  Adjunctive use with oestrogen in postmenopausal women with an intact uterus (for hormone replacement therapy [HRT])

Vaginal Route

- Prevention of preterm birth in women with a singleton pregnancy who have a short cervix and/or a history of spontaneous preterm birth
- Luteal phase support
  Supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles

4.2 Dose and method of administration

Dosage

The recommended dose is as follows, according to the indication and the administration route:

Oral Route

- ***In the treatment of menopause***: In women receiving estrogen replacement therapy there is an increased risk of endometrial cancer which can be countered by progesterone administration. The recommended dose is 200 mg/day at bedtime at least 12 to 14 days per month, i.e. on days 15 to 26 of each cycle or in the last 2 weeks of each treatment sequence of oestrogen therapy followed by approximately one week without any replacement therapy and during which withdrawal bleeding may occur.

  Alternatively 100 mg can be given at bedtime, from days 1 to 25 of each cycle, withdrawal bleeding being less with this treatment schedule.

Vaginal Route

- ***In the Luteal Phase Support during Assisted Reproductive Technology (ART)****:* the recommended dosage is 600 mg/day, in three divided doses, from the evening after the day of oocyte retrieval or latest the day of embryo transfer until at least the 7th week of pregnancy and not later than the 12th week of pregnancy.
- For prevention of preterm birth in women with a singleton pregnancy who have a short cervix and/or a history of spontaneous preterm birth, the recommended dosage is 200 mg per day in the evening at bedtime from around week 20 to week 34 of pregnancy.

Method of Administration

This product is intended for oral or vaginal use.

Oral Route

UTROGESTAN 200 mg should not be taken with food; it is preferable to take the capsules in the evening at bedtime. Concomitant food ingestion increases the bioavailability of micronized progesterone.

Each capsule of UTROGESTAN 200 mg must be swallowed with a little water.

Vaginal Route

Each capsule of UTROGESTAN 200 mg must be inserted deep into the vagina.

Paediatric Use

There is no relevant use of UTROGESTAN 200 mg in the paediatric population in the indications listed above.

Use in the Elderly

There is no relevant use of UTROGESTAN 200 mg in the elderly population in the indications listed above.

4.3 Contraindications

This medicinal product must not be used in the following situations:

- Hypersensitivity to the active substances, soya, progesterone or to any of the excipients listed in section 6.1).
- Jaundice
- Severe hepatic dysfunction,or a history of liver disease as long as liver function tests have failed to return to normal
- Known, past or Suspected breast or genital tract carcinoma.

- Undiagnosed vaginal bleeding.
- Thrombophlebitis or thromboembolic disorders (e.g. deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders.
- Cerebral haemorrhage.
- Porphyria.
- Missed abortion
- Premature rupture of membranes (PPROM)

4.4 Special warnings and precautions for use

- For all indications:
- Under the recommended conditions for use, this treatment is NOT A CONTRACEPTIVE.
- A complete medical examination must be performed before starting and regularly during the treatment.
- Any vaginal bleeding should always be investigated
- Utrogestan 200 mg Capsules contains soybean lecithin and may rarely cause hypersensitivity reactions and bronchospasm (urticarial and anaphylactic shock in hypersensitive patients). As there is a possible relationship between allergy to soya and allergy to peanut, patients with peanut allergy should avoid using Utrogestan 200mg Capsules.

For HRT indication:

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision (for HRT indication)

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised.

- conditions that might be aggravated by fluid retention (e.g. hypertension, cardiac disease, renal disease)
- in patients with a history of depression, migraines, (severe) headaches or photosensitivity.
- Leiomyoma (uterine fibroids) or endometriosis
- Liver disorders (e.g. liver adenoma)
- Otosclerosis
- Diabetes melitus with or without vascular involvement
- Cholelithiasis
- Systemic lupus erythematosus
- Risk factors for thromboembolic disorders (see below)
- A history of endometrial hyperplasia (see below)
- Epilepsy

- Asthma

Reasons for immediate withdrawal of therapy (for HRT indication)

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Sudden or gradual, partial or complete loss of vision
- Proptosis or diplopia
- Papilloedema
- Retinal vascular lesions

Endometrial hyperplasia and carcinoma

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and estrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

The addition of progesterone for at least 12 days per month/28 day cycle or continuous combined estrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with estrogen-only HRT.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding persists a lower dose of Utrogestan for 25 days per cycle could be considered (see section 4.2).

If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined estrogen-progestagen and possibly also estrogen-only HRT, that is dependent on the duration of taking HRT.

Combined estrogen-progestagen therapy

- The randomised placebo-controlled trial the (Women's Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progestagen for HRT that becomes apparent after about 3 years (see Section 4.8).

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

HRT, especially estrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of estrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller, risk (see Section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), *i.e.* deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).
- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).
- Generally recognised risk factors for VTE include, use of estrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.
  As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).
  If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (*e.g*, antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.
- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (*e.g.* painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT.

Combined oestrogen-progestagen therapy

- The relative risk of CAD during use of combined oestrogen+progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Ischaemic stroke

Combined estrogen-progestagen and estrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Other conditions

HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.

Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis or hepatocellular liver disease.

Warning specific for supplementation of the luteal phase during Assisted Reproductive Technology cycles:

Utrogestan should only be used during the first three months of pregnancy and must only be administered by vaginal route.

Precautions specific for prevention of preterm birth in women with a singleton pregnancy who have a short cervix and/or a history of spontaneous preterm birth:

Before treatment is initiated:

- The risks and benefits of the options available, should be discussed with the patient. The physician and patient should make a shared decision on which treatment is most suitable.
- Premature rupture of membranes (PPROM) should be excluded. Should rupture of membranes occur during treatment, further treatment with Utrogestan 200 mg should be discontinued.

4.5 Interaction with other medicines and other forms of interaction

- Potent hepatic enzyme CYP450-3A4 inducers such as barbiturates, anti-epileptics (phenytoin, carbamazepine), phenylbutazone, spironolactone and griseofulvin, some antibiotics (ampicillins, tetracyclines) may increase the hepatic metabolism and the elimination of progesterone.
- Herbal products containing St John's wort (Hypericum perforatum) may increase metabolism and the elimination of progesterone.
- On the contrary ketokonazole and other inhibitors of CYP450-3A4 such as ritonavir and nelfinavir may increase bioavailability of progesterone. The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC50 <0.1 µM)
- Utrogestan 200 mg may interfere with the effects of bromocriptine and may raise the plasma concentration of ciclosporin. Utrogestan 200 mg may affect the results of laboratory tests of hepatic and/or endocrine functions.
- Metabolism of utrogtestan 200 mg is accelerated by rifamycin medicines (such as rifampicin) and antibacterial agents.
- The clinical relevance of the in vitro findings is unknown.

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

Effect on laboratory tests

UTROGESTAN 200 mg may affect the results of laboratory tests of hepatic and/or endocrine functions.

4.6 Fertility, pregnancy and lactation

Pregnancy

Australian categorisation definition of Category A:

For HRT indication

Oral Utrogestan 200mg Capsules are not indicated during pregnancy.
If pregnancy occurs during medication, Utrogestan 200mg Capsules should be withdrawn immediately.
Clinically, data on a large number of exposed pregnancies indicate no adverse effects of progesterone on the foetus. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of estrogens + progesterone indicate no teratogenic or foetotoxic effect.
Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.

For all other indications

No association has been found between the maternal use of natural progesterone in early pregnancy and foetal malformations.

Breastfeeding

UTROGESTAN 200 mg is not indicated during breast-feeding. Detectable amounts of progesterone enter the breast milk.

Fertility

For HRT indication

Not relevant

For all other indications

As this medicinal product is indicated to support luteal deficiency in sub-fertile or infertile women, there is no deleterious known effect on fertility.

4.7 Effects on ability to drive and use machines

UTROGESTAN 200 mg capsules may cause dizziness in a minority of patients if taken orally; therefore caution is advised in drivers and users of machines. These problems can be avoided by taking the capsules at bedtime.

4.8 Undesirable effects

The following effects have been seen by oral route administration:

System organ class	Common undesirable effects	Uncommon adverse effects	Rare undesirable effects	Very rare undesirable effects

	≥1/100; <1/10	≥1/1000; ≤1/100	≥1/10000; ≤1/1000	≤1/10000
Reproductive system and breast disorders	Altered periods Amenorrhoea Intercurrent bleeding	Mastodynia		
Nervous system disorders	Headaches	Drowsiness Dizziness		Depression
Gastrointestinal disorders		Vomiting Diarrhoea Constipation	Nausea	
Hepatobiliary disorders		Cholestatic jaundice		
Immune system disorders				Urticaria
Skin and subcutaneous tissue disorders		Pruritus Acne		Chloasma

Somnolence or transient dizziness may occur 1 to 3 hours after intake of the drug. Bedtime dosing and reduction of the dose may reduce these effects.

For vaginal administration:

Local intolerance (burning, itching or oily discharge) has been observed in clinical studies and has been reported in publications, but the incidence is extremely rare.

When used as recommended, transient fatigue or dizziness may occur within 1 – 3 hours of taking the medicine

Adverse effects have been ranked under the headings of frequency using the following convention: very common (≥1/10); common (1/100 to 1/10); uncommon (≥1/1000 to <1/100); rare (≥ 1/10,000 to< 1/1,000); very rare (1/10,000); frequency not known (cannot be estimated from the available data)

System organ class (SOC)	**Frequency Not known (cannot be estimated from the available data)**
Skin and subcutaneous tissue disorders	Pruritus
Reproductive system and breast disorders	Vaginal haemorrhage Vaginal discharge
General disorders and administrative site conditions	Burning sensation

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Symptoms of overdosage may include somnolence, dizziness, euphoria or dysmenorrhoea. Treatment is observation and, if necessary, symptomatic and supportive measures should be provided.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system; Progestogens: Pregen-(4) derivatives

ATC code: G03DA04

Mechanism of action

Progesterone is the natural progestogen, the main hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase. UTROGESTAN capsules have all the properties of endogenous progesterone with induction of a full secretory endometrium and in particular gestagenic, antiestrogenic, slightly antiandrogenic and antialdosterone effects.

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

Prevention of preterm birth

Progesterone is important during pregnancy in maintaining uterine quiescence by limiting the production of stimulatory prostaglandins responsible for uterine contractions.

Progesterone also limits the release of matrix metalloproteinases that can cause cervical effacement and softening by inhibiting the expression of contraction-associated protein genes (ion channels, oxytocin and prostaglandin receptors, and gap junctions) within the myometrium.

Although levels of progesterone in the maternal circulation do not change significantly in the weeks preceding labour, the onset of labour at term and preterm is associated with a functional withdrawal of progesterone activity at the level of the uterus.

Clinical efficacy/safety studies

HRT indication

As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of progesterone greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Prevention of preterm birth

A meta-analysis of individual participant data from randomised controlled trials (EPPPIC 2021) concluded that vaginal progesterone reduced birth before 34 weeks gestation in high-risk singleton pregnancies. Trials in singleton pregnancies included mostly women with previous spontaneous preterm birth or short cervix. Preterm birth before 34 weeks was reduced in such women who received vaginal progesterone (nine trials, 3769 women; relative risk (RR) 0.78, 95% CI 0.68 – 0.90). Given increased underlying risk, absolute risk reduction was greater for women with a shorter cervix, hence treatment might be most useful for these women. Shared decision making with women with high-risk singleton pregnancies should discuss an individual's risk, potential benefits, harms and practicalities of intervention. Treatment of unselected multifetal pregnancies with progestogen was not supported by evidence.

5.2 Pharmacokinetic properties

Absorption

Oral Administration

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 (200 mg), plasma progesterone levels increased to reach the C_{max} of 13.8 ng/mL +/- 2.9 ng/mL in 2.2 +/- 1.4 hours. The elimination half-life observed was 16.8+/- 2.3 hours.

Vaginal Administration

The pharmacokinetic profile of different dosage (e.g. 300 mg vs. 600 mg) of progesterone administered into the vagina is non-linear. Systematic progesterone concentrations are the same with different dosages, because of local pharmacokinetic processes, such as direct passive diffusion or transport through the local blood circulation or lymph circulation, due to which progesterone will be transported from the vagina to the womb.

Following vaginal administration, micronised progesterone is absorbed rapidly and achieves higher stable plasma levels in the range of 4-12 ng/ml, depending on the daily dose, and a average C_{max} at around the 8 hour mark is achieved with much less inter-subject variation than following oral administration.

With a 600 mg daily dose of progesterone administered into the vagina the progesterone concentration in plasma were stable throughout administration times so that the highest average concentration was 11.63 ng/ml.

Distribution Progesterone is transported via the lymph and blood vessels and approximately 96-99% bound to serum proteins, primarily to serum albumin (50-54%) and transcortin (43-48%).

Micronised progesterone administered into the vagina undergoes the first metabolic cycle in the womb, when progesterone distributes primarily or selectively into the womb, causing higher hormone levels in the womb and nearby tissues.

Elimination

Urinary elimination is observed for 95% in the form of glycurone conjugated metabolites, mainly 3 a, 5 ß–pregnanediol (pregnandiol).

Oral progesterone is excreted via the gallbladder and kidneys, with a half-life of 5- 95 minutes.

By administering progesterone into the vagina, the first pass metabolism in the liver can be avoided, which enables concentrations in plasma to remain higher for longer.

Biotransformation Progesterone is metabolised primarily by the liver. Following oral administration, the main plasma metabolites are 20 a hydroxy- Δ 4 a- prenolone and 5 a-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.
It is detectable in urine after 24 hours, and a small amount (8-17%) is secreted in the faeces.

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

Linearity/non-linearity
The pharmacokinetics of micronized progesterone is independent of the dose administered. Although there were inter-individual variations, the individual pharmacokinetic characteristics were maintained over several months permitting appropriate individual adaptation of the posology and indicating predictable responses to the drug.

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule contents: sunflower oil, soya lecithin (fully refined)
Capsule shell: gelatin, glycerol, titanium dioxide

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30°C.
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Each box contains 15 or 42 units of 200 mg soft capsule packed in blister strips.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Telephone: 09 377 3336

9 DATE OF FIRST APPROVAL

2 April 2013

10 DATE OF REVISION OF THE TEXT

November2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2.0	Clarification that the soy lecithin is fully refined. Addition of sulfite as excipient with known effect
4.4	Update to warning regarding hypersensitivity reactions as per EMA guidelines
4.9	Update to wording regarding management of overdose
6.4	Removal of storage condition “Do not refrigerate”