Professional information for UTROGESTAN and UTROGESTAN 200 mg

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

UTROGESTAN, 100 mg capsules

UTROGESTAN 200 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

UTROGESTAN: Each soft gelatine capsule contains 100 mg of micronised progesterone.

UTROGESTAN 200 mg: Each soft gelatine capsule contains 200 mg of micronised progesterone.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

UTROGESTAN: Round-shaped, slightly yellow, soft gelatine capsule (8,5 mm diameter) containing an oily whitish suspension (paste).

UTROGESTAN 200 mg: Ovoid-shaped, slightly yellow, soft gelatine capsule (length: 15,05 mm, width: 9,1 mm) containing an oily whitish suspension (paste).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral route:

Disorders associated with progesterone deficiency, in particular:

- premenstrual syndrome
- menstrual irregularities due to dysovulation or anovulation

- mastopathy
- perimenopause
- hormone replacement therapy for menopause (in addition to oestrogen therapy).

Vaginal route:

- progesterone support during ovarian insufficiency or complete ovarian failure in women lacking ovarian function (oocyte donation)
- supplementation of the luteal phase during *in-vitro* fertilisation (IVF) cycles
- supplementation of the luteal phase during spontaneous or induced cycles, in cases of sub-fertility or primary or secondary infertility, particularly due to dysovulation
- in cases of threatened miscarriage or prevention of recurrent miscarriage due to luteal phase deficiency, until week 12 of pregnancy.
- prevention of preterm birth in women with singleton pregnancy who have a short cervix (mid-trimester sonographic cervix ≤ 25 mm) and/or a history of spontaneous preterm birth.

For all other indications of progesterone, the vaginal route represents an alternative to the oral route in cases of:

- side effects caused by progesterone (drowsiness following absorption via the oral route).

4.2 Posology and method of administration

Posology

It is important to adhere strictly to the recommended dosages for all therapeutic indications.
The dosage must not exceed 200 mg per dose, regardless of the indication and route of administration (oral or vaginal).

Oral route:

For progesterone deficiency, an average dose of 200 mg – 300 mg UTROGESTAN per day is recommended.

- **For luteal phase insufficiency** (premenstrual syndrome, mastopathy, irregular menstruation

and perimenopause), the usual therapeutic regimen is 200 mg – 300 mg per day:

- a single dose of 200 mg in the evening, upon going to bed, or
- 300 mg split over two doses.

Ten days per cycle, usually from day 17 to day 26, inclusive.

- **When used as a hormone replacement therapy for menopause**, oestrogen therapy alone is not advised (due to the risk of endometrial hyperplasia). Instead, UTROGESTAN should be incorporated at a dose of 200 mg per day:
  - split over two 100-mg doses, or
  - as a single 200-mg dose in the evening, upon going to bed, either from day 12 to day 14 of the month, or during the last two weeks of each treatment course.

  Following this treatment, all replacement therapies should be suspended for approximately one week, during which time it is normal to observe withdrawal bleeding.

  For these indications, the vaginal route should be used, at the same dosage as for the oral route, in the event of side effects caused by UTROGESTAN (drowsiness following oral absorption).

Vaginal route:

- **Progesterone replacement therapy in cases of ovarian insufficiency or complete ovarian failure in women lacking ovaries** (oocyte donation).

  The therapeutic regimen (in addition to appropriate oestrogen therapy) is as follows:
  - 100 mg UTROGESTAN per day on days 13 and 14 of the transfer cycle, then
  - 200 mg of UTROGESTAN per day on days 15 and 25 of the transfer cycle, split over one or two doses per day, then
  - from day 26 of the cycle, and in cases of an incipient pregnancy, the dose may be increased up to a maximum of 600 mg per day, split over three doses.

  This dosage should be adhered to until day 60, or until week 12 of pregnancy at the latest.

- **Supplementation of the luteal phase during IVF cycles:**

  The recommended dosage is 400 mg – 600 mg per day, over two to three doses per day, from the date of HCG injection until week 12 of pregnancy.

- **Supplementation of the luteal phase in cases of spontaneous or induced cycles, in subjects with sub-fertility or primary or secondary sterility, particularly due to dysovulation:** The recommended dosage is 200 mg –300 mg per day, over two doses, for ten days, from day 17 of the cycle. If menstruation does not resume and pregnancy is diagnosed, treatment should be quickly resumed until week 12 of pregnancy.

- **Threatened early miscarriage or repeated miscarriage due to luteal phase insufficiency:** The recommended dosage is 200 mg – 400 mg per day, split over two doses, until week 12 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

Oral route:

It is recommended to take UTROGESTAN sometime after eating, preferably in the evenings upon going to bed.

Vaginal route:

Each capsule should be inserted deep into the vagina.

4.3 Contraindications

- Known sensitivity to progesterone or any of the excipients listed in section 6.1.
- Severe liver disease such as cholestatic jaundice, or hepatitis, or a history of severe liver disease, hepatic cell tumours, Rotor syndrome, or Dubin-Johnson syndrome.
- Undiagnosed vaginal bleeding.
- Mammary or genital tract carcinoma.
- Conditions of rare occurrence known to be affected by sex steroids i.e. herpes gestationis, jaundice of pregnancy, otosclerosis, severe pruritus, or porphyria.
- Previous or current thromboembolism disorders (*e.g.* deep venous thrombosis, pulmonary embolism) or thrombophlebitis.
- Known thrombophilic disorders.
- Cerebral haemorrhage.
- Breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Treatment should be discontinued if the results of liver function tests become abnormal or if cholestatic jaundice appears.

More than half early spontaneous abortions are due to genetic defects. Moreover, infections and mechanical disorders may cause early miscarriages. In these cases the only effect of progesterone administration will be to delay the expulsion of the dead egg (or interruption of a terminated pregnancy).

Treatment should be discontinued upon diagnosis of a missed abortion.

A pre-treatment physical examination prior to the initiation of hormone replacement treatment should include special attention to breast and pelvic organs as well as Papanicolaou smear.

The use of UTROGESTAN must be reserved for cases with insufficient secretion of the corpus luteum.

Treatment under the recommended conditions of use is not contraceptive.

The use of UTROGESTAN during pregnancy is restricted to the first trimester via the vaginal route.

UTROGESTAN, when taken orally, is not suitable for the treatment for the threat of preterm birth.

Exceptional cases of cytolytic hepatitis and intrahepatic cholestasis of pregnancy have been reported in patients using UTROGESTAN, during the second and third trimesters of pregnancy.

UTROGESTAN contains soybean lecithin and may cause hypersensitivity reactions (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.

4.5 Interaction with other medicines and other forms of interaction

Enzyme inducers

The efficacy of UTROGESTAN may be decreased due to an enhanced metabolism of progesterone by hepatic enzyme inducing medicines, such as carbamazepine, phenobarbital, phenytoin, rifabutin or rifampicin, griseofulvin, some antibiotics (ampicillin, tetracyclines), and herbal products containing St. John's wort (*Hypericum perforatum)*.

Enzyme inhibitors

Hepatic metabolic enzyme inhibitors such as ketoconazole, ritonavir, nelfinavir may increase the bioavailability of UTROGESTAN.

Effect of UTROGESTAN on other medicines

UTROGESTAN may increase the plasma concentration of ciclosporin, theophylline and troleandomycin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. The use of UTROGESTAN during pregnancy is restricted to the vaginal application.

Cases of hepatic cytolysis and cases of cholestasis of pregnancy have been reported during administration of micronised progesterone during the 2nd and 3rd trimesters of pregnancy.

Breastfeeding

The use of UTROGESTAN during breastfeeding is not recommended. See section 4.3.

Fertility

UTROGESTAN is indicated to support luteal deficiency in sub fertile or infertile women**.**

4.7 Effects on ability to drive and use machines

Patients intending to drive or use machines should be warned that they may suffer from drowsiness, dizziness and vertigo after administration of UTROGESTAN. Patients experiencing drowsiness, dizziness, or vertigo during treatment with UTROGESTAN should avoid driving or use of machines.

4.8 Undesirable effects

Summary of the safety profile

The reporting rate of adverse drug reactions with UTROGESTAN oral and vaginal formulations was calculated as 1,43/1 000 patient year's corresponding to approximately 1,5 spontaneously reported cases in every 1 000 patients exposed to UTROGESTAN.

List of adverse reactions

Oral route:

Blood and lymphatic system disorders

Frequent: Hyperglycaemia.

Less frequent: Thromboembolism or thrombus formation.

Immune system disorders

Frequency unknown: Anaphylaxis or anaphylactoid reaction.

Endocrine disorders

Less frequent: Cushing's syndrome, adrenal suppression or insufficiency.

Metabolism and nutrition disorders

Frequent: Unusual or rapid weight gain.

Nervous system disorders

Frequent: Dizziness, drowsiness, fatigue, mild headache, mood changes, nervousness, unusual tiredness or weakness, vertigo, somnolence.

Less frequent: Mental depression, insomnia.

Vascular disorders

Frequent: Oedema.

Less frequent: Hypotension, hot flushes.

Gastrointestinal disorders

Frequent: Abdominal cramping or pain, abdominal bloating, diarrhoea, nausea.

Hepato-biliary disorders

Frequency unknown: Jaundice.

Skin and subcutaneous tissue disorders

Less frequent: Skin rash, acne, loss or gain of body, facial or scalp hair; melasma, chloasma, pruritus.

Musculoskeletal and connective tissue disorders

Frequent: Joint pain.

Frequency unknown: Loss of bone mineral density, osteoporosis, osteoporotic fracture.

Renal and urinary disorders

Frequent: Urinary problems.

Reproductive system and breast disorders

Frequent: Amenorrhoea, breakthrough menstrual bleeding or metromenorrhagia, menorrhagia, spotting.

Less frequent: Galactorrhoea, breast pain or tenderness, libido decrease.

Frequency unknown: Vaginal haemorrhage.

General disorders and administration site conditions

Frequency unknown: Fatigue.

Vaginal route:

- No local intolerances (such as burning, pruritus or fatty discharge) have been observed during various clinical trials.
- No general side effects, including drowsiness or transient feelings of dizziness, have been reported during clinical studies, at the recommended dosages.

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

Skin and subcutaneous tissue disorders

Frequency unknown: Pruritus.

Reproductive system and breast disorders

Frequency unknown: Vaginal haemorrhage, vaginal discharge.

Description of selective adverse reactions

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.

The following risks apply in relation to systemic oestrogen/progestogen treatment:

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-
  progestogen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study (MWS)– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5-year period*2	Risk ratio & 95 % CI	Additional cases per 1000 HRT users over 5 years (95 % CI)
Oestrogen only HRT			
50 – 65	9 – 12	1,2	1 – 2 (0 – 3)
Combined oestrogen-progestogen			
50 – 65	9 – 12	1,7	6 (5 – 7)
# Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on			

use.

Note: Since the background incidence of breast cancer differs by region, the number of additional cases of breast cancer will also change proportionately

2 **Taken from baseline incidence rates in developed countries*

US WHI studies – additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95 % CI	Additional cases per 1000 HRT users over 5 years (95 % CI)
CEE oestrogen study			
50 – 79	21	0,8 (0,7 – 1.0)	-4 (-7 – 0)*3
CEE+MPA oestrogen & progestogen‡			
50 – 79	17	1,2 (1,0 – 1,5)	+4 (0 – 9)

‡ When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

3 **WHI study in women with no uterus, which did not show an increase in risk of breast cancer*

Endometrial cancer risk

Postmenopausal women with a uterus.

The endometrial cancer risk is about 5 in every 1 000 women with a uterus not using hormone replacement therapy (HRT).

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding progesterone to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study (MWS) the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1,0 (0,8 – 1,2)).

Ovarian cancer

Use of oestrogen-only and combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (HRT (RR 1,43, 95% CI 1,31 – 1,56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2 000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 will be diagnosed with ovarian cancer over a 5-year period**.**

Risk of venous thromboembolism

HRT is associated with a 1,3 - .3-fold increased relative 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 using HT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95 % CI	Additional cases per 1000 HRT users.
Oral oestrogen-only*4			
50 – 59	7	1,2 (0,6 – 2,4)	1 (-3 – 10)
Oral combined oestrogen-progestogen			
50 – 59	4	2,3 (1,2 – 4,3)	5 (1 – 13)

4 Study in women with no uterus*

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestogen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

The use of oestrogen-only and oestrogen + progestogen therapy is associated with an up to 1,5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke*5 over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95 % CI	Additional cases per 1000 HRT users.
50 – 59	8	1,3 (1,1 – 1,6)	3 (1 – 5)
5 no differentiation was made between ischaemic and haemorrhagic stroke*			

The following adverse reactions have also been reported in association with systemic oestrogen/progestogen treatment:

- Rash.
- Urticaria.
- Chloasma/melasma.
- Pyrexia.
- Insomnia.

- Alopecia.
- Irregular menstruation.
- Amenorrhoea.
- Breast pain/mastodynia.
- Fluid retention/oedema.
- Weight changes.
- Changes in libido.
- Depression.
- Gall bladder disease.
- Probable dementia over the age of 65 (see section 4.4).
- Skin and subcutaneous disorders: erythema multiforme, erythema nodosum, vascular purpura.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of UTROGESTAN is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/health-products-vigilance/

4.9 Overdose

Symptoms of overdosage may include nausea, vomiting, somnolence, dizziness, fatigue euphoria or dysmenorrhoea. Treatment of overdosage consists of discontinuation of UTROGESTAN together with institution of appropriate symptomatic and supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.8.2 Progesterone with or without oestrogens

Pharmacotherapeutic groups: Genitourinary system and sex hormones, Sex hormones and modulators of the genital system, ATC codes: G03DA04

The properties of progesterone are comparable to those of natural progesterone, in particular being a progestogen, oestrogen antagonist, mild androgen antagonist, and aldosterone antagonist.

Mechanism of action

Progesterone is a 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 have all the properties of endogenous progesterone, in particular gestagenic, anti-oestrogenic, slightly anti-androgenic and anti-aldosterone effects.

Clinical efficacy and safety

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

5.2 Pharmacokinetic properties

Oral route

Absorption:

Micronised progesterone is absorbed by the digestive tract.

Blood progesterone levels begin to rise within the first hour, and plasma levels reach the highest levels within one to three hours of a dose.

Pharmacokinetic studies conducted in volunteers have shown that, after simultaneously consuming

two capsules of progesterone 100 mg, on average, blood progesterone levels rise from 0,13 ng/mL to 4,25 ng/mL after one hour, to 11,75 ng/mL after two hours, to 8,37 ng/mL after four hours, to 2 ng/mL after six hours, and to 1,64 ng/mL after eight hours.

Given the hormone retention time by tissues, in order to ensure infusion for a full 24 hours, it seems necessary to split the dosage over two doses, spaced approximately 12 hours apart.

There are discernible individual variations, although a given individual will exhibit the same pharmacokinetic characteristics for several months, thus allowing individuals to adapt to the dosage.

Distribution

Progesterone is approximately 96 % - 99 % bound to serum proteins, primarily to serum albumin (50 % - 54 %) and transcortin (43 % - 48 %).

Metabolism:

Progesterone is metabolised primarily by the liver. The main plasma metabolites are 20α-hydroxyprogesterone, Δ4α-prenolone and 5α-dihydroprogesterone.

Elimination

Ninety-five per cent is eliminated via the urine in the form of glucuronide-conjugated metabolites, of which the principal metabolite is 3α, 5β-pregnanediol (pregnanediol). These plasma and urine metabolites are identical to those physiologically secreted from the corpus luteum in the ovaries.

Vaginal route

Absorption:

Following vaginal insertion, progesterone is rapidly absorbed by the vaginal mucosa, as shown by the rise in plasma progesterone levels within one hour of administration.

The maximum plasma progesterone concentration is reached two to six hours after insertion, and remains at an average concentration of 9,7 ng/mL over the 24 hours following the administration of 100 mg in the morning and evening. This recommended average dose therefore leads to stable,

physiological plasma progesterone concentrations similar to those observed during the luteal phase of a normal ovulatory menstrual cycle. Small inter-individual variations in progesterone levels make it possible to accurately predict the expected effect of a standard dose.

At doses of more than 200 mg per day, the resulting progesterone concentrations are comparable with those described during the first trimester of pregnancy.

Metabolism:

The plasma concentration of 5β-pregnanolone does not increase.

It is primarily 3α, 5β-pregnanediol (pregnanediol) that is eliminated via the urine, as demonstrated by the gradual increase in its concentration (until reaching a maximum concentration of 142 ng/mL after six hours). Following vaginal administration, only low plasma levels of pregnanolone and 5α-dihydroprogesterone are detected.

5.3 Preclinical safety data

Non-clinical 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

Gelatine

Glycerol

Soybean lecithin

Sunflower oil

Titanium dioxide (E171)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Protect from light and excessive moisture.

Do not remove from outer carton until required for use.

6.5 Nature and contents of container

UTROGESTAN: PVC/aluminium or PVC/PVDC/aluminium blisters with 15 capsules, each carton containing 30 capsules.

UTROGESTAN 200 mg: PVC/aluminium or PVC/PVDC/aluminium blisters with 15 capsules, each carton containing 15 capsules.

6.6 Special precautions for disposal and other handling

UTROGESTAN does not require any special storage conditions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Medi Challenge (Pty) Ltd

493 De Jonge Street

Elardus Park

Pretoria

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Tel: 011 462 5491

8. REGISTRATION NUMBERS

UTROGESTAN: 29/21.8.2/0215

UTROGESTAN 200 mg: A40//21.8.2/0771

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

UTROGESTAN: 17 February 1999

UTROGESTAN 200 mg: 30 September 2011

10. DATE OF REVISION OF THE TEXT

13 June 2024