UTROGESTAN 100mg capsules

Progesterone

1 PRODUCT NAME

UTROGESTAN 100MG CAPSULES

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Soft, round, slightly yellow capsule containing a whitish oily suspension of 100 mg progesterone (micronised).

Excipient(s) with known effect: Soya lecithin

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsules, soft

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

UTROGESTAN 100 mg capsule is indicated in adults, *via* the oral route, for:

Hormone replacement therapy

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

4.2 Dose and method of administration

Dosage

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

Oral Route

- ***In the treatment of menopause:*** oestrogen alone therapy is not recommended on its own in menopausal women with an intact uterus. The usual 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 therapyfollowed 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.

Method of Administration

This product is intended only for oral use.

UTROGESTAN 100 mg should not be taken with food; it is preferable to take the capsules in the evening at bedtime.

Oral Route
Each capsule of UTROGESTAN 100 mg must be swallowed with a little water.

Paediatric Use
There is no relevant use of UTROGESTAN 100 mg in the paediatric population in the indications listed above.

Use in the Elderly
There is no relevant use of UTROGESTAN 100 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 progesterone or to any of the excipients listed (see Pharmaceutical Precautions section).
- Severe liver dysfunction.
- Suspected or confirmed breast or genital organ neoplasia.
- Undiagnosed vaginal bleeding.
- Thromboembolic or thrombophlebitis disorders.
- Cerebral haemorrhage.
- Porphyria.

4.4 Special warnings and precautions for use
Under the recommended conditions for use, this treatment is **NOT A CONTRACEPTIVE**.

If the treatment sequence is started too early in the month, particularly before the 15th day of the cycle, the cycle may be shortened or bleeding may occur.

- Patients must be monitored closely if they have a past history of venous thrombosis
- If uterine bleeding is present, do not prescribe before establishing a cause, particularly with endometrial investigations.
- Because of the metabolic risks and risks of thromboembolism which cannot be entirely excluded, administration should be discontinued in the event of:
    - Occular disorders such as reduced vision, diplopia and retinal vascular lesions;
    - Venous thromboembolic or thrombotic events, regardless of location;
    - Severe headaches
- If the patient develops amenorrhoea during treatment, ensure that she is not pregnant.

UTROGESTAN 100mg Capsules are intended to be co-prescribed with an oestrogen product as HRT. Epidemiological evidence suggests that the use of HRT is associated with an increased risk of developing deep vein thrombosis (DVT) or pulmonary embolism. The prescribing information for the co-prescribed oestrogen product should be referred to for information about the risks of venous thromboembolism.

There is suggestive evidence of a small increased risk of breast cancer with oestrogen replacement therapy. It is not known whether concurrent progesterone influences the risk of cancer in post-

menopausal women taking hormone replacement therapy. The prescribing information for the co-prescribed oestrogen product should be referred to for information about the risks of breast cancer.

Precautions

Prior to taking hormone replacement therapy (and at regular intervals thereafter) each woman should be assessed. A personal and family medical history should be taken and physical examination should be guided by this and by the contraindications and warnings for this product. UTROGESTAN 100mg Capsules should not be taken with food and should be taken at bedtime. Concomitant food ingestion increases the bioavailability of UTROGESTAN 100mg Capsules.

UTROGESTAN 100mg Capsules 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 breastfeeding mothers.

Clinical examination of the breasts and pelvic examination should be performed where clinically indicated rather than as a routine procedure. Women should be encouraged to participate in the national breast cancer screening programme (mammography) and the national cervical cancer screening programme (cervical cytology) as appropriate for their age. Breast awareness should also be encouraged and women advised to report any changes in their breasts to their doctor or nurse.

UTROGESTAN 100 mg contains soya lecithin and may cause hypersensitivity reactions (urticarial and anaphylactic shock).

UTROGESTAN 100 mg is not a treatment for premature labour.

4.5 Interaction with other medicines and other forms of interaction

Progesterone administration for a minimum of 12 days per cycle is strongly recommended in oestrogen hormone therapy for postmenopausal women with an intact uterus.

The combination with other medicinal products may increase progesterone metabolism which may alter its effect. This applies to:

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

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.

Effect on laboratory tests

UTROGESTAN 100 mg may affect the results of laboratory tests of hepatic and/or endocrine functions.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category A)

Australian categorisation definition of Category A:

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

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

Breastfeeding

There is insufficient information on the excretion of progesterone/metabolites in human milk. Secretion of progesterone into breast milk has not been studied in detail. UTROGESTAN 100 mg should not be used during lactation.

Fertility

Progesterone did not show evidence of genotoxicity in *in vitro* studies for point mutations or for chromosomal damage. It 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. 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.

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.

4.7 Effects on ability to drive and use machines

UTROGESTAN 100 mg has minor influence on the ability to drive and used machines.

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 Undesirable effects

The following effects have been seen by oral route administration:

System organ class	Common undesirable effects ≥1/100; <1/10	Uncommon adverse effects ≥1/1000; ≤1/100	Rare undesirable effects ≥1/10000; ≤1/1000	Very rare undesirable effects ≤1/10000
Reproductive system and breast disorders	Altered periods Amenorrhoea Intercurrent bleeding	Mastodynia		
Nervous system disorders	Headaches	Drowsiness Fleeting dizzy sensations		Depression
Gastrointestinal disorders		Vomiting Diarrhoea Constipation	Nausea	
Hepatobiliary disorders		Cholestatic jaundice		
Immune system disorders				Urticaria
Skin and subcutaneous tissue disorders		Pruritus Acne		Chloasma

Drowsiness and/or fleeting dizzy sensations are seen particularly with concomitant hypoestrogenism. These effects disappear immediately without compromising the benefit of treatment when doses are reduced or oestrogenism is increased.

If the treatment sequence is started too early in the month, particularly before the 15th day of the cycle, the cycle may be shortened or intercurrent bleeding may occur.

Changes in periods, amenorrhoea or intercurrent bleeding have been observed and associated with the use of progesterone in general.

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

The adverse effects described above are usually signs of overdose. These disappear without treatment when the dosage is reduced.

The usual dosage may be excessive in some people because of persistence or recurrence of unstable endogenous progesterone secretion, particular sensitivity to the substance or excessively low concomitant blood oestradiol concentrations. In these situations:

- The dosage should be reduced or the progesterone should be administered AT BEDTIME IN THE EVENING, 10 days per cycle, if drowsiness or fleeting dizziness occurs.
- Treatment should be started later in the cycle (such as on day 19 instead of day 17) if the cycle is shortened or spotting occurs.

- Check that oestradiol concentrations are sufficient in the perimenopausal period and in hormone-replacement therapy for menopause.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

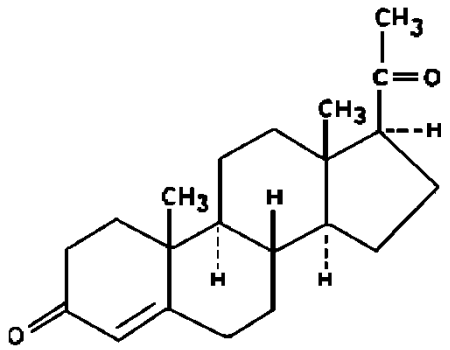
Pharmacotherapeutic group: Genitourinary system and sex hormones

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.

Progesterone



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

Molecular formula: $C_{21}H_{30}O_2$.

MW: 314.5

CAS: 57-83-0.

Micronised progesterone is a white or almost white crystalline powder or colourless crystals. The form used in UTROGESTAN is the alpha-crystalline form, and has a melting point of 126°C - 131°C.

Progesterone is practically insoluble in water, freely soluble in ethanol and sparingly soluble in acetone and in fatty oils.

The capsules contain the following active ingredient: Progesterone (micronised) 100 mg. They also contain sunflower oil, soya lecithin, gelatin, glycerol and titanium dioxide.

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 (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.

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

Distribution

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

Elimination

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

Metabolism

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.

5.3 Preclinical safety data

Carcinogenicity

Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. 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 PARTICULARS

6.1 List of excipients

Capsule contents: sunflower oil, soya lecithin

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.

Do not refrigerate.

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Each box contains 15 or 30 units of 100 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

17 January 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatted to new SPC format