

# NEW ZEALAND DATA SHEET

## 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 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.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used.

##### ***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.

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## **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:

- Known hypersensitivity to progesterone or to any of the excipients listed (see Pharmaceutical Precautions section).
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Known, past or suspected breast cancer.
- Known or suspected estrogen-dependent malignant tumours (e.g. genital tract carcinoma/endometrial cancer)
- Undiagnosed genital bleeding.
- Previous or current venous thromboembolism (e.g. deep venous thrombosis, pulmonary embolism) or thrombophlebitis.
- Untreated endometrial hyperplasia
- Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency, see section 4.4)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Cerebral haemorrhage has been observed with synthetic progestagens.
- Porphyria.

## **4.4 Special warnings and precautions for use**

### **General warnings**

Utrogestan is **NOT A CONTRACEPTIVE** and must only be used in accordance with the indications in section 4.1.

### **Reasons for immediate withdrawal of therapy**

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
- HRT indication only: Pregnancy

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- Sudden or gradual, partial or complete loss of vision
- Venous or thrombotic thromboembolic accidents regardless of the territory

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:
  - Ocular 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. Pregnancy should be excluded before initiating 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.

### **Venous thromboembolism**

Patients with known thrombophilic states have an increased risk of venous thromboembolism (VTE) and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

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. 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)

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.

### **Endometrial hyperplasia and carcinoma**

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.

### 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

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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 in hypersensitive patients). As there is a possible relationship between allergy to soya and allergy to peanuts, patients with peanut allergies should avoid using Utrogestan.

Utrogestan contains highly refined oil, for which the incidence of hypersensitivity is very rare in adults.

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.

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## 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.

HRT indication: Pregnancy should be excluded before initiating HRT. If pregnancy occurs during the use of oral Utrogestan 100 mg capsules, treatment should be withdrawn immediately.

### **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<br>≥1/100; <1/10 | Uncommon<br>≥1/1000; ≤1/100 | Rare ≥1/10000;<br>≤1/1000 | Very rare<br>≤1/10000 |
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| <b>Metabolism and nutrition disorders</b>              | Weight fluctuation                           | Fluid retention,   |                  |  |
| <b>Psychiatric disorders</b>                           | Insomnia                                     | Agitation, anxiety, Apathy, Depression, Disorientation, Mood swings, Nervousness   | Change in libido |  |
| <b>Reproductive system and breast disorders</b>        | Intermenstrual bleeding, Vaginal haemorrhage | Abnormal withdrawal bleeding, Breast discomfort, Endometrial hyperplasia, Vaginal discharge, Vulvovaginal discomfort, Menstrual cycle abnormal |                  |  |
| <b>Nervous system disorders</b>                        | Dizziness, Headaches, Somnolence             | Amnesia, Migraine, Paraesthesia, Speech disorder, Syncope  |                  |  |
| <b>Eye disorders</b>                                   |  | Vision disturbances  | Eye irritation   |  |
| <b>Ear and labyrinth disorders</b>                     |  | Tinnitus, Vertigo  |                  |  |
| <b>Cardiac disorders</b>                               |  | Palpitations, Tachycardia  |                  |  |
| <b>Vascular disorders</b>                              |  | Haemorrhage, Hot flush, Hypotension,   |                  |  |
| <b>Respiratory, thoracic and mediastinal disorders</b> |  | Dyspnoea   |                  |  |
| <b>Gastrointestinal disorders</b>                      | Abdominal distention, Abdominal pain, nausea | Vomiting, Diarrhoea, Constipation  |                  |  |
| <b>Hepatobiliary disorders</b>                         |  | Cholestatic jaundice   |                  |  |
| <b>Skin and subcutaneous tissue disorders</b>          | Pruritus                                     | Acne, Alopecia, Erythema, Hyperhidrosis, Rash, Urticaria   |                  |  |

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| <b>Musculoskeletal and connective tissue disorders</b>      |                  | Arthralgia, Back pain, Limb discomfort, muscle spasms, Myalgia |         |  |
| <b>Renal and urinary disorders</b>                          |                  |  | Dysuria |  |
| <b>General disorders and administration site conditions</b> | Fatigue, Malaise | Asthenia, Chest discomfort (including pain), Oedema            |         |  |

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 15<sup>th</sup> 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://pophealth.my.site.com/carmreportnz/s/s/>

### 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

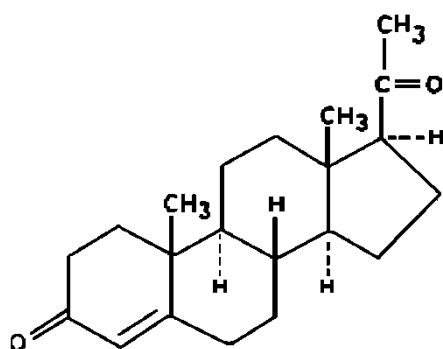
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ATC code: G03DA04

## **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.



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## **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 glycoconjugated metabolites, mainly 3 $\alpha$ , 5 $\beta$ -pregnanediol (pregnandiol).

## **Metabolism**

Progesterone is metabolised primarily by the liver. Following oral administration, the main plasma metabolites are 20 $\alpha$  hydroxy- $\Delta$  4 $\alpha$ -pregnenolone and 5 $\alpha$ -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

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## 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

March 2025

[CCDS Dec 2023 Ver 5]

## SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information  |
|-----------------|---|
| 4.2             | Clarification of wording regarding dosage to reflect currently registered indications |