SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of medicinal product:

Utrogestan 100
Utrogestan 200

2. Qualitative and Quantitative composition:

Utrogestan 100: Each soft gelatin capsule contains 100 mg of progesterone in a micronized form.
Utrogestan 200: Each soft gelatin capsule contains 200 mg of progesterone in a micronized form.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

oral or vaginal capsule.

4. Clinical Particulars

4.1.Therapeutic Indications

Vaginal or oral administration:
Disorders related to progesterone deficit in particular menopause (in association with estrogen therapy).
Vaginal administration:
Progesterone substitution for ovary deprived women in situation of total progesterone deficiency.
Supplementation of the luteal phase during in vitro fertilization cycles. Supplementation of the luteal phase during spontaneous or induced cycles, in cases of hypofertility or primary or secondary ovarain failure, particulary through dysovulation. In cases of threatning abortion or prevention of repeated abortions due to proven luteal insufficiency. For all other progesterone indications, in the case of : Adverse events due to progesterone, contraindication of the oral route of administration hepatopathy.

4.2. Posology and method of administration

The recommended dosages should be strictly observed.
Whatever the indication and route of administration (oral or vaginal), the dosage should never exceed 200mg per dose.

Oral administration
This medicinal product should be taken on an empty stomach preferably in the evening before going to bed.
Usually, the dosage is 200 to 300 mg of progesterone daily in two intakes: one in the morning, preferably 2 hours after breakfast, another one to two in the evening (at bedtime) , on an empty stomach.

In luteal insufficiency (premenstrual syndrome, benign mastopathy, menstrual irregularities), dose is from 200 to 300 mg daily:
- either 200 mg in one intake at bedtime,
- or 300 mg in two intakes.
for 10 days per cycle, usually from the 17th to the 26th day, inclusive.

For the premenopause: the dose is 300 mg daily, divided into two intakes, i.e., 100 mg preferably two hours after breakfast and 200 mg at bedtime for 10 days (from the 17th to the 26th day of the cycle) up to 20 days (from the 7th to the 26th day of the cycle).

For menopause (HRT):
Isolated therapy is not recommended (risk of endometrial hyperplasia). Progesterone is therefore combined at a dose of 200 mg .
The usual dose is 200 mg daily for 12 to 14 days per month, if the patient does not wish to have regular cyclic bleeding. The total daily dose should be taken at bedtime in conjunction with estrogen administered at the lowest effective dose (i.e. that which induces a mean E2 plasma level above 60 pg/ml). The great majority of patients will become amenorrheic during the first year of treatment.

This treatment must be followed by the total discontinuation of any replacement therapy for approximately one week during which a deprivation hemorrhage is often observed.

If the patient wishes to have regular cyclic bleeding, the dose is 300 mg daily for 10 days per month, divided into two intakes, i.e. 100 mg in the morning and 200 mg at bedtime. The estrogen dose has to be increased (i.e. 3 mg percutaneous 17β estradiol per day).

In these indications the vaginal route is used, at the same dosages as the oral route, in cases of side effects due to progesterone (drowsiness after oral absorption).

Vaginal administration
the capsules must be inserted deep into the vagina.

On the average, the dosage is 200 mg of progesterone daily distributed into two doses: one in the morning, another one in the evening.

In case of partial luteal insufficiencies (dysovulation, menstrual irregularities), the treatment should be carried out during 10 days per cycle, usually from the 17th to the 26th day, on the basis of 200 mg per day.

Progesterone substitution of ovary deprived women during complete deficiency (donation of ovocytes): progesterone dose is 100 mg on the 13th and 14th days of the transfer cycle, then 200 mg per day 15th to the 25th day of the cycle in one or two intakes. From the 26th day, the dose is increased in case of onset of pregnancy by 100 mg per day each week reaching a maximum of 600 mg per day divided into 3 intakes. This dosage will be continued until the 60th day and until the 12th week of pregnancy and no further.

Supplementation of the luteal phase during IVF, 400 mg-600 mg per day, in two to three divided doses, starting on the evening of the HCG injection until the 12th week of pregnancy.

During the threat of abortion or prevention of repeated abortion due to luteal insufficiency, the recommended dose is 200 mg to 400 mg per day in 2 intakes until the 12th week of amenorrhea and no further.

Supplementation of the luteal phase during spontaneous or induced cycles, in cases of hypofertility or primary or secondary sterility, particularly through dysovulation. The recommended posology is from 200 mg to 300 mg per day in two intakes, from the 17th day of the cycle during 10 days. The treatment must be repeated, as soon as possible, in the case of amenorrea and diagnosis of pregnancy until the 12th week of pregnancy.

4.3. Contraindications

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

- severe liver dysfunction.
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- suspected or confirmed breast or genital organ neoplasia.

4.4. Special Warnings and Special precaution 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.

- 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 territory;
    - severe headaches
- Patients should be monitored closely if they have a past history of venous thrombosis.
- If a patient develops amenorrhoea during treatment, ensure that she is not pregnant.

More than 50% of the early spontaneous abortions are due to genetic complications. Infectious and mechanical disorders can also cause early miscarriage: the only effect of progesterone in this situation is to delay removal of a deceased embryo. Progesterone should therefore be limited to situations in which corpus luteum secretion is insufficient.

UTROGESTAN should only be used in pregnancy during the first trimester and only by the vaginal route. UTROGESTAN is not a treatment of threatening premature labour.

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

4.5. Interactions with other medicinal products and other forms of interaction

Progesterone administration for a minimum of 12 days per cycle is strongly recommended in oestrogen hormone therapy for the menopause.

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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Use of this medicine is not contraindicated in pregnancy, including the first weeks of pregnancy.

Lactation

Secretion of progesterone into breast milk has not been studied in detail. It should therefore be avoided in women who are breast-feeding.

4.7. Effects on the Ability to Drive and Use Machines

Cases of drowsiness and dizziness have been reported with oral use.

Attention should be drawn to the risks of drowsiness and/or dizziness associated with the oral use of this medicine, particularly in the case of patients who drive or operate machinery. Ingestion of the capsules at bedtime will avoid such problems.

4.8. Undesirable effects:

Oral administration:
The following effects have been seen:

System organ class	Common undesirable effects ≥1/100; <1/10	Uncommon undesirable effects ≥1/1000; ≤1/100	Rare undesirable effects ≥1/10 000; ≤1/1 000	Very rare undesirable effects ≤1/10 000
Reproductive system and breast disorders	-Altered periods -Amenorrhoea -Intercurrent bleeding	-Mastodynia		
Central 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 progesterones in general.

Vaginal administration
Despite the possibility of local irritation may occur (soya lecithin), no significant local intolerance (burning, pruritus or greasy discharge) has been observed during different clinical trials.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9. Overdosage

Oral administration
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 oestrodiol 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 oestrodiol concentrations are sufficient in the perimenopausal period and in hormone-replacement therapy for the menopause.

Vaginal administration
Despite the fact that no overdose has been reported to date with the vaginal form, the undesirable effects described above could be signs of an overdose. They resolve spontaneously when the dosage is reduced.

5. Pharmacological Properties

5.1. Pharmacodynamic properties:

Pharmacotherapeutic group: Sex and urogenital system hormones
ATC Code: G03DA04

UTROGESTAN, which contains micronised progesterone, significantly raises plasma progesterone concentrations after oral use. It therefore corrects progesterone deficiencies.

5.2. Pharmacokinetic properties

Oral administration

Blood concentrations of progesterone rise from the first hour after dosing and the highest plasma concentrations are found 1 to 3 hours after dosing. Because of the hormone tissue retention time, the daily dosage appears to need to be divided into two separate doses 12 hours apart in order to achieve hormone exposure throughout the 24 hour period.

Metabolism: the plasma and urinary metabolites are identical to those found following physiological secretion from the ovarian corpus luteum: in plasma these are mostly 20-alpha hydroxy delta-4 pregnenolone and 5-alpha dihydroprogesterone. 95% of urinary excretion is in the form of glycuronoconjugated metabolites, the major one of which is 3 alpha-5 beta pregnanediol (pregnandiol).

Vaginal administration

Elevation of blood progesterone levels starts from the first hour onwards, with peak plasma levels observed 1 to 3 hours after administration.

At the average recommended dose, **stable** physiological levels of plasma progesterone, similar to those obtained during the luteal phase of a normal, ovulatory menstrual cycle, can be reached and maintained.

Thus, Utrogestan Vaginal soft capsules induce adequate endometrial maturity, promoting the implantation of a potential embryo.
At higher doses, increased gradually, this route of administration makes it possible to achieve blood progesterone levels similar to those observed during the first trimester of pregnancy.

Metabolism: plasma and urinary metabolites are identical to those found during physiological secretion of corpus luteum in the ovaries: in plasma, its main metabolites are 20-alpha-hydroxy-delta-4-pregnenolone and 5-alpha-dihydroprogesterone. Urinary elimination occurs at a rate of 95% in the form of glucuronide-conjugated metabolites, the main one being 3-alpha-5-beta pregnanediol (pregnandiol).

5.3. Preclinical Safety data

Information not provided.

6. Phramaceutical Particulars

6.1. List of excipients

Capsule contents: Sunflower oil, soya lecithin.
Capsule coating: Gelatin, glycerin, titanium dioxide, purified water

6.2. Incompatibilties

Not applicable

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage:
Store below 25°C

6.5. Nature and contents of container:
Utrogestan 100: 30 capsules in thermoformed blister pack (PVC/Aluminium)
(2 blisters of 15 capsules each)
Utrogestan 200: 15 capsules in thermoformed blister pack (PVC/Aluminium)
(2 blister of 7 and 8 capsules)

6.6. Instructions for use and handling
No special requirements

7. Manufacturer

Besins International Laboratories
3 Rue du Bourge L'Abbe
75003 Paris, France.

8. License Holder and Marketing Authorization Holder:

CTS Ltd.
4 Haharash Street
Hod Hasharon
Israel

Revised in 08/2021 according to the MoH guidelines