INSTRUCTION for medical use
UTROGESTAN

Composition:
active ingredient: progesterone;
each capsule contains natural micronized progesterone 100 or 200 mg;
excipients: peanut oil, soya lecithin, gelatin, glycerine, titanium dioxide.

Pharmaceutical form. Capsules.

ATC code G03D A04.

Clinical characteristics

Indications.
Disorders related to progesterone deficiency.

Oral route
Premenstrual syndrome, menstrual irregularities (disovulation, anovulation); fibrous-cystic mastopathy; preclimacteric period; hormone replacement therapy in menopause (in combination with estrogen therapy); infertility in luteal insufficiency; prevention of habitual miscarriage due to luteal insufficiency; menace of preterm delivery.

Intravaginal route
A decrease of the ability of being fertilized in primary or secondary infertility due to partial or complete luteal insufficiency (dysovulation, support of the luteal phase during preparation for extracorporeal fertilization, program of oocyte donation); prevention of habitual miscarriage or threat of spontaneous miscarriage in luteal insufficiency).

Contraindications
Severe liver impairment; allergy to any component of the product.

Administration and dosage
Duration of treatment depends on the character of the disease.

Oral route
In most cases the average daily dose is 200-300 mg in 2 divided doses (200 mg in evening, at bedtime, and 100 mg in the morning in case of necessity).

In luteal phase insufficiency (premenstrual syndrome, menstrual irregularities, premenopause, fibrous-cystic mastopathy): take for 10 days (from the 17th through the 26th day of the cycle).

In hormone replacement therapy of menopause: since estrogen therapy alone is not recommended, progesterone may be used as a supplement to it in the last two weeks of each therapeutic cycle which follow a one-week support of any replacement treatment during which withdrawal bleeding can be observed.

At the threat of preterm delivery take 400 mg of Utrogestan every 6-8 hours till disappearance of symptoms. The efficacious dose and regimen are selected individually depending on clinical manifestations of the threat of preterm delivery. After disappearance of symptoms the product may be used till 36 weeks of pregnancy.

Intravaginal route
Capsules must be inserted deep into the vagina.
On the average the dose is 200 mg progesterone a day (1 capsule of 200 mg or 2 capsules of 100 mg, divided into 2 doses, in the morning and in the evening, which are inserted deep into the vagina, if necessary, by means of an applicator. It may be increased depending on the patient's reaction.
In partial insufficiency of the luteal phase (dysovulation, menstrual irregularities,) the daily dose is 200 mg for 10 days (from the 17th through the 26th day of the cycle).

In complete insufficiency of the luteal phase:
the complete absence of progesterone in women with non-functioning (absent) ovaries (oocyte donation): the progesterone dose is 100 mg in the morning and in the evening from the 15th through the 25th day of the cycle. Beginning from the 26th day, in case of early diagnosis of pregnancy, the dose increases by 100 mg a day, reaching the maximum of 600 mg/day divided into 3 doses. This dose should be used till the 60th day.

Support of the luteal phase during the cycle of extracorporeal fertilization: in a dose of 600 mg a day divided into 3 doses (a single dose of 200 mg every 8 hours).

At the threat of miscarriage or for prevention of habitual miscarriages in progesterone insufficiency: 200-400 mg a day (100-200 mg as a single dose every 12 hours) till 12 weeks of pregnancy.

Side reactions.
The following side events are observed during oral use:

<table>
<thead>
<tr>
<th>System</th>
<th>Common side events</th>
<th>Uncommon side events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital</td>
<td>- a change in the menstrual cycle &lt;1/100; &lt;1/10</td>
<td></td>
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<tr>
<td></td>
<td>- amenorhea</td>
<td></td>
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<tr>
<td></td>
<td>- bleedings in the middle of the cycle</td>
<td></td>
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<tr>
<td>Nervous</td>
<td>- headache</td>
<td>- drowsiness</td>
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<td></td>
<td></td>
<td>- transient episodes of dizziness</td>
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<tr>
<td>Hepatobiliary</td>
<td></td>
<td>- cholestatic jaundice</td>
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<td></td>
<td></td>
<td>- pruritis</td>
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<td></td>
<td></td>
<td>- gastrointestinal disturbances</td>
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</tbody>
</table>

Drowsiness and/or transient sensations of dizziness are observed especially in associated hypoestrogenia. A decrease of the product dose or a decrease of the estrogen dose immediately eliminated these phenomena without reducing the therapeutic effect.

If the course of treatment is initiated too early at the beginning of the month cycle, especially before the 15th day, a reduction of the cycle of accidental bleedings may occur.

On the whole, during the use of progestins changes of menstruation, amenorrhea or a bleeding in the middle of the cycle can be observed.

During intravaginal use: no side effects were found.

Overdose
The above described symptoms of a side effect result as a rule from overdose. They disappear spontaneously at a decrease of the dose.

In some persons an usual dose can prove to be excessive due to the existing or secondary manifesting unstable endogenous secretion of progesterone, increased sensitivity to the product or a very low associated level of estradiol in blood; in such cases it is enough:

- to reduce the dose of progesterone or to prescribe taking progesterone in the evening at bedtime for 10 days in case of drowsiness or transient episodes of dizziness.
- to postpone the beginning of treatment for a later day of the cycle (for example, to the 19th day instead of the 17th day) in case of its shortening or spotting;
- it should be checked whether the level of estradiol is sufficient in the patient who is receiving hormone replacement therapy during menopause.

Use during pregnancy or breast feeding
During the period of using the product not a single case of adverse effect of the product on the fetus was observed.
If the product is used in the second or third trimesters of pregnancy, the control of the liver function is necessary. The penetration of progesterone into the breast milk has not been studied precisely. Therefore, it is better to avoid the drug usage during breast feeding.

**Peculiarities of use.**
The treatment in the recommended doses does not possess the contraceptive effect. If the course of treatment begins too early at the beginning of the month cycle, especially before the 15th day of the cycle, a shortening of the cycle or bleeding may be observed. If uterine bleedings occur, the product should not be administered without establishing their causes, in particular, by examining the endometrium. Because of the thromboembolic and metabolic risk which cannot be completely excluded, the product should be discontinued in case of occurrence of the following:

- visual disorders such as loss of vision, diplopia, vascular lesions of the retina;
- thromboembolic venous or thrombotic complications, irrespective of the area of lesion;
- severe headache.

If the patient has the thrombophlebitic history, she has to be closely monitored. If amenorrhea occurs during treatment, it is necessary to check, if there is no pregnancy. More than half of early spontaneous abortions are caused by genetic complications. Infectious manifestations and mechanical disorders can also cause early abortions; the only ground of prescribing progesterone in this case is the delay of expulsion of the dead egg. Thus, administration of progesterone according to the doctor's recommendation should be envisaged for the cases when progesterone secretion is insufficient.

Purified peanut oil can contain proteins of peanuts. The European Pharmacopeia does not have the method of analysis of residual proteins.

**Ability to influence quickness or reaction while driving or operating machines**
Drivers of vehicles or operators of machines can experience drowsiness and episodes of dizziness related to oral administration of the product.

**Interaction with other medicinal products and other types of interaction**
If for treatment of the threatening preterm delivery Utrogestan is combined with beta-adrenomimetics, the doses of the latter may be decreased. At the concomitant use with inductors of hepatic enzymes (barbiturates, phenytoin, rifampicin, phenylbutazone, spironolactone, griseofulvin) or antibiotics (ampicillins, tetracyclines) an increase or decrease of the progesterone concentration in plasma are possible. Progestins decrease tolerance to glucose that may require an increase of the daily dose of insulin and other antidiabetic agents in patients with diabetes mellitus.

**Pharmacodynamic properties**

*Pharmacodynamics.*
The pharmacological properties of the product are related to progesterone, one of the hormones of corpus luteum, which contributes to formation of normal secretory endometrium in women. Causes transition of the uterine mucous membrane from the phase of proliferation to the secretory phase, and after fertilization contributes to its transition to the state necessary for development of the fertilized oocyte. Decreases excitability and contractility of the uterine musculature and uterine tubes. Does not possess the androgenic activity. Exerts the blocking effect on secretion of the hypothalamic factors of release of LG and FSG. Suppresses the formation by hypophysis of gonadotropic hormones and ovulation.

*Pharmacokinetics.*

*Oral use*
The increased level of progesterone in plasma is observed from the first hour after absorption of the product in the gastrointestinal tract. The maximum level of progesterone in plasma is observed 1-3 hours after the intake of the product (after 1 hour – 4.25 ng/ml, after 2 hours - 11.75 ng/ml, after 4 hours - 8.37 ng/ml, after 6 hours - 2.00 ng/ml and 1.64 ng/ml after 8 hours). The main metabolites of progesterone in plasma are 20α-hydroxy,δ-4α-pregnelone and 5α-dihydroprogesterone. The product is excreted in the urine, mainly as 3α,5β-pregnadiol. The metabolites determined in the urine and plasma are similar to the metabolites which are formed during physiological secretion of corpus luteum.

**Pharmaceutical characteristics.**

*Main physicochemical substances:*

- **capsules 100 mg:** round, soft, shiny gelatin capsules, somewhat yellowish in color, containing whitey oil suspension;
- **capsules 200 mg:** oval, soft, shiny gelatin capsules, somewhat yellowish in color, containing whitish oil suspension.

*Shelf life* 3 years.

**Storage.** Keep out of the reach of children at a temperature not exceeding 25°C.

**Package**

Capsules 100 mg - 15 soft capsules in each blister, 2 blisters in each cardboard box.
Capsules 200 mg - 7 soft capsules in each blister, 2 blisters in each cardboard box.

**How dispensed.** Prescription medicine.

Manufacturer. Besins Manufacturing Belgium.

**Location.** 128, Groot-Bijgaardenstraat, 1620 Drogenbos, Belgium.

**Date of the last review:**

Harmonized with the materials of the registration dossier and credibly known data on the product use.