

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Utrogestan Vaginal 100 mg Soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100 mg progesterone (*micronised*).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal soft capsules.

Round and slightly yellow soft capsules, containing whitish oily suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Utrogestan Vaginal 200 mg Capsules is indicated in women for

- Supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles.
- Prevention of preterm birth in women with a singleton pregnancy who have a short cervix (mid-trimester sonographic cervix ≤ 25 mm) and/or a history of spontaneous preterm birth

4.2 Posology and method of administration

Posology

On average, the dosage is 200 mg progesterone per day (i.e. one 200 mg capsule or two 100 mg capsules spread over two doses, one in the morning and one in the evening), to be inserted deep into the vagina, possibly with the aid of an applicator. This can be increased depending on the patient's response.

- For **luteal phase deficiency** (poor ovulation, menstrual irregularities): the treatment is used for 10 days per cycle, usually from **days 17 to 26** inclusive, at a rate of 200 mg progesterone per day.
- In cases of **infertility with total luteal phase deficiency (egg donations)**: the progesterone dose is 100 mg progesterone on days 13 and 14 of the transfer cycle, then 100 mg progesterone on the morning and evening of days 15 to 25 of the cycle. From day 26 onwards, the dose is increased - in the event of conception - by 100 mg progesterone per day each week, reaching a maximum of 600 mg progesterone per day, spread over three doses. This dosage is maintained up until day 60.
- For **luteal phase supplementation during IVF**: treatment is initiated starting

from the evening of the transfer, at a rate of 600 mg progesterone spread over three doses: morning, noon and evening.

- For **threatened miscarriages or in the prevention of recurrent miscarriages due to luteal phase deficiency**: the average dosage is 200 mg to 400 mg progesterone per day, spread over two doses, up until week 12 of pregnancy.

Method of administration

Vaginal administration: the capsules must be inserted deep inside the vagina.

4.3 Contraindications

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

- serious changes in liver function.
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- neoplasm of the breast or genital organs, suspected or confirmed.

4.4 Special warnings and precautions for use

This treatment, under the recommended conditions of use, **IS NOT CONTRACEPTIVE**.

If the treatment schedule is initiated too early in the month, particularly before day 15 of the cycle, this may shorten the cycle and/or bleeding may occur.

The woman must insert each capsule deep into the vagina.

- In the case of uterine bleeding, do not prescribe until a definite cause has been established, preferably via endometrial investigation.
- Due to the thromboembolic and metabolic risks which cannot totally be eliminated, treatment must be discontinued at the onset of:
 - eye disorders, such as loss of vision, diplopia, vascular lesions of the retina;
 - venous thromboembolisms or thrombotic events, regardless of the region;
 - severe headaches.
- Patients with a history of thrombophlebitis should be closely monitored.
- If amenorrhoea should occur during treatment, pregnancy must be excluded.

More than half of spontaneous abortions are due to genetic complications. Furthermore, infectious manifestations and mechanical disorders may be responsible

for miscarriages; in which case, the sole effect of administering progesterone would be a delay in the expulsion of a dead ovum. Progesterone administration must therefore only be reserved for cases where corpus luteum secretion is insufficient.

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

4.5 Interaction with other medicinal products and other forms of interaction

Combination with other medicinal products may reduce the metabolism of progesterone, which may lead to a modification in its effect.

This applies in the case of:

- potent enzyme inducers such as barbiturates, antiepileptic agents (phenytoin), rifampicin, phenylbutazone, spironolactone and griseofulvin. These medicines cause increased metabolism in the liver.
- certain antibiotics (ampicillin, tetracyclines): variations in the intestinal flora, leading to a change in the enterohepatic circulation of steroids.

Since these interactions can differ depending on the individual, it is not always possible to predict clinical results.

Progestins may cause a reduction in glucose tolerance and, as a result, may increase the need for insulin and other antidiabetic agents in patients with diabetes.

Smoking may reduce the bioavailability of progesterone and alcohol abuse may increase it.

4.6 Fertility, pregnancy and lactation

The use of UTROGESTAN VAGINAL Soft capsules is not contraindicated during pregnancy, including the first few weeks (see section 4.1: Therapeutic indications - Obstetric).

The passage of progesterone into milk has not been studied in detail. Its prescription should therefore be avoided during the breastfeeding period.

4.7 Effects on ability to drive and use machines

Cases of drowsiness and dizziness have been reported with the oral route.

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

Despite the possibility that local irritation may occur (soya lecithin), no significant local intolerance (burning, pruritus or greasy discharge) has been observed during various clinical studies.

The following effects have been reported with soft capsules administered **via the oral route**:

| System organ class | Common undesirable effects ≥1/100; <1/10 | Uncommon undesirable effects ≥1/1,000; | Rare undesirable effects ≥1/10,000; | Very rare undesirable effects ≤1/10,000 |
|---|--|--|---|---|
| Reproductive system and breast disorders | Altered menstrual cycles Amenorrhoea | Mastodynia | | |
| Nervous system disorders | Headache | Drowsiness Transient | | Depression |
| Gastrointestinal disorders | | Vomiting Diarrhoea | Nausea | |
| Hepatobiliary disorders | | Cholestatic jaundice | | |
| Immune system | | | | Urticaria |
| Skin and subcutaneous tissue | | Pruritus Acne | | Chloasma |

Drowsiness and/or transient dizziness are observed particularly with concomitantly low levels of oestrogen. These effects are immediately reversible upon reduction of the dosage or escalation of the oestrogen dose, without compromising the therapeutic benefit.

If the treatment schedule is initiated too early in the month, particularly before day 15 of the cycle, this may shorten the cycle or intermenstrual bleeding may occur.

Altered menstrual cycles, amenorrhoea and intermenstrual bleeding have been observed and reported in association with general progestin use.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

In some individuals, the usual dosage may prove to be too high, as evidenced by the persistence or recurrence of unstable endogenous progesterone secretion, marked sensitivity to the product or concomitantly low blood levels of oestradiol. In these cases, the following measures should be taken:

- In the event of drowsiness or transient dizziness, the dosage amount should be reduced or progesterone should be administered IN THE EVENING AT BEDTIME, over 10 days per cycle.

- In the event of spotting/shortening of the menstrual cycle, initiation of treatment should be deferred until later into the cycle (e.g. day 19 instead of day 17).
- Perimenopausal women/women receiving HRT should be tested to ensure that blood oestradiol levels are sufficient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Genitourinary system and sex hormones
ATC code: G03DA04

Utrogestan Vaginal Soft capsules, containing progesterone in micronised form, allows a significant increase in plasma progesterone levels following vaginal administration, thus making it possible to correct progesterone deficiency.

5.2 Pharmacokinetic properties

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 corpus luteum secretion: 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

No data supplied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents: sunflower oil, soya lecithin.

Capsule shell: gelatin, glycerol, titanium dioxide (E171), purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Three years in the sealed blister.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

Boxes of 30 or 90 x 100 mg soft capsules, packed in PVC/Aluminium blisters, for vaginal use.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Besins Manufacturing S.A.
Avenue Louise, 287
1050 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBERS

TAN 20 350

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25th September, 2020

10. DATE OF REVISION OF THE TEXT

Not applicable (First authorization)