SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Utrogestan Vaginal 200 mg Soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

200 mg progesterone (micronised).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal soft capsules.

Utrogestan Vaginal 200 mg: Ovoid 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

For **supplementation of the luteal phase during Assisted Reproductive Technology cycles** - the recommended dosage is 600 mg/day, in three divided doses, from the day of embryo transfer until at least the 7th week of pregnancy and not later than the 12th week of pregnancy.

For **prevention of preterm birth in women with a singleton pregnancy who have a short cervix and/or a history of spontaneous preterm birth**, the recommended dosage is 200 mg per day in the evening at bedtime from around week 20 to week 34 of pregnancy.

Paediatric *population*

There is no relevant use of Utrogestan Vaginal 200 mg Capsules in the paediatric population.

Older *people*

There is no relevant use of Utrogestan Vaginal 200 mg Capsules in older people.

Method of Administration:

Vaginal

Each capsule of Utrogestan Vaginal 200mg must be inserted deep into the vagina.

Method of administration

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

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
• Severe hepatic dysfunction,
• Undiagnosed vaginal bleeding,
• Mammary or genital tract carcinoma,
• Thrombophlebitis,
• Thromboembolic disorders,
• Cerebral haemorrhage,
• Porphyria.
• Missed abortion

4.4 Special warnings and precautions for use

Warnings:
Utrogestan Vaginal 200mg Capsules should only be used during the first three months of pregnancy and must only be administrated by vaginal route.
Utrogestan Vaginal 200mg Capsules is not suitable as a contraceptive.
Treatment should be discontinued upon diagnosis of a missed abortion.

Precautions:
Utrogestan Vaginal 200 mg Capsules 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 peanut, patients with peanut allergy should avoid using Utrogestan Vaginal 200mg Capsules.

4.5 Interaction with other medicinal products and other forms of interaction

Utrogestan Vaginal 200mg Capsules may interfere with the effects of bromocriptine and may raise the plasma concentration of ciclosporin. Utrogestan Vaginal 200mg Capsules may affect the results of laboratory tests of hepatic and/or endocrine functions.
Metabolism of Utrogestan Vaginal 200mg Capsules is accelerated by rifamycin medicines (such as rifampicin) and antibacterial agents.

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC50 <0.1 μM). Ketoconazole is a known inhibitor of cytochrome P450 3A4. These data therefore suggest that ketoconazole may increase the bioavailability of progesterone. The clinical relevance of the in vitro findings is unknown.

4.6 Fertility, pregnancy and lactation

Pregnancy
No association has been found between the maternal use of natural progesterone in early pregnancy and foetal malformations.
Breastfeeding
Utrogestan Vaginal 200 mg Capsules is not indicated during breast-feeding.
Detectable amounts of progesterone enter the breast milk.
Fertility
As this medicinal product is indicated to support luteal deficiency in sub-fertile or infertile women, there is no deleterious known effect on fertility.

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; ≤1/100	Rare undesirable effects ≥1/10,000; ≤1/1,000	Very rare undesirable effects ≤1/10,000
Reproductive system and breast disorders	Altered menstrual cycles Amenorrhoea Intermenstrual bleeding	Mastodynia		
Nervous system disorders	Headache	Drowsiness Transient dizziness		Depression
Gastrointestinal disorders		Vomiting Diarrhoea Constipation	Nausea	
Hepatobiliary disorders		Cholestatic jaundice		
Immune system				Urticaria
Skin and subcutaneous tissue disorders		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 30ºC. Store in the original package.

6.5 Nature and contents of container

Boxes of 15 or 45 x 200 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 20 406

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25th September, 2020

10. DATE OF REVISION OF THE TEXT

Not applicable (First authorization)