Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Utrogestan Vaginal 200 mg vaginal capsule, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg progesterone (micronised).
Excipients with known effect: Soya lecithin

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Vaginal Capsule, soft

Ovoid and slightly yellow soft capsules, containing whitish oily suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Utrogestan Vaginal 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 (see section 4.4).

4.2 Posology and method of administration

Posology
For **supplementation of the luteal phase during Assisted Reproductive Technology cycles**-the recommended dose is 600 mg/day, given in three divided doses, one in the morning, one at midday and the third at bedtime. The treatment is started not later than the third day after oocyte retrieval. If pregnancy has been confirmed, continue treatment until at least the 7th week but no longer 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. For information on shared decision making, see section 4.4.

Paediatric population
There is no relevant use of Utrogestan Vaginal in the paediatric population.

Elderly patients
There is no relevant use of Utrogestan Vaginal in the elderly.

MethodofAdministration:
Vaginal
Each capsule of Utrogestan Vaginal must be inserted deep into the vagina.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- Jaundice,
- Severe hepatic dysfunction,
- Undiagnosed vaginal bleeding,

- Mammary or genital tract carcinoma,
- Thrombophlebitis,
- Thromboembolic disorders,
- Cerebral haemorrhage,
- Porphyria,
- Missed abortion,
- Premature rupture of membranes (PPROM) (see Section 4.4),
- Allergy to peanuts or soya (see Section 4.4).

4.4 Special warnings and precautions for use

Warnings:

- A complete medical examination must be performed before starting and regularly during the treatment.
- Utrogestan Vaginal is not suitable as a contraceptive.
- In rare cases, the use of micronized progesterone during the second and third trimester of pregnancy may lead to the development of gravidic cholestasis or hepatocellular liver disease.
- Treatment should be discontinued upon diagnosis of a missed abortion.

Precautions:

- Any vaginal bleeding should always be investigated.

Warnings specific for supplementation of the luteal phase during Assisted Reproductive Technology cycles:

- Utrogestan Vaginal should only be used during the first three months of pregnancy and must only be administrated by vaginal route

Precautions specific for prevention of preterm birth in women with a singleton pregnancywho have a short cervix and/or a history of spontaneous preterm birth:

Before treatment is initiated:

- The risks and benefits of the options available, should be discussed with the patient. The physician and patient should make a shared decision on which treatment is most suitable (see section 5.1).
- Premature rupture of membranes (PPROM) should be excluded (see section 4.3). Should rupture of membranes occur during treatment, further treatment with Utrogestan Vaginal should be discontinued.

Utrogestan Vaginal contains soyabean 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 (see Section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Utrogestan Vaginal may interfere with the effects of bromocriptine and may raise the plasma concentration of ciclosporin. Utrogestan Vaginal may affect the results of laboratory tests of hepatic and/or endocrine functions.

Metabolism of Utrogestan Vaginal is accelerated by rifamycin medicines (such as rifampicin) and antibacterial agents.

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC_{50}<0.1 microM 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

Natural progesterone may be given orally, vaginally or by the intramuscular route to treat luteal phase deficiency until at least the 7th week of pregnancy and not later than the 12th week of pregnancy. Natural progesterone may also be given vaginally for prevention of preterm birth, from the 20th week of pregnancy to the 34th week of pregnancy.

Pregnancy
No association has been found between the maternal use of natural progesterone in early pregnancy and foetal malformations.

Breastfeeding
Utrogestan Vaginal 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

Utrogestan Vaginal has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Local intolerance (burning, itching or oily discharge) has been observed in clinical studies and has been reported in publications, but the incidence is extremely rare.
When used as recommended, transient fatigue or dizziness may occur within 1 – 3 hours of taking the medicine.
Reporting of suspected adverse reactions after authorisation
The information given below is based on extensive post marketing experience from vaginal administration of progesterone.
Adverse effects have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

Systemorgan class (SOC)	**Frequency Not known (cannot be estimated from the available data)**
Skin and subcutaneous tissue disorders	Pruritus
Reproductive system and breast disorders	Vaginal haemorrhage Vaginal discharge
General disorders and administrative site conditions	Burning sensation

Reportingof suspected adversereactions
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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; Website: www.hpra.ie.

4.9 Overdose

Symptoms of overdosage may include somnolence, dizziness, euphoria or dysmenorrhoea. Treatment is observation and, if necessary, symptomatic and supportive measures should be provided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progestogens, ATC code: G03DA04.

Mechanism of action

Supplementation of the luteal phase during ART:

Progesterone is a natural progestogen, the main hormone and most important hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase. Utrogestan Vaginal have all the properties of endogenous progesterone with induction of a full secretory endometrium and in particular gestagenic, antiestrogenic, slightly anti-androgenic and antialdosterone effects.

Prevention of preterm birth

Progesterone is important during pregnancy in maintaining uterine quiescence by limiting the production of stimulatory prostaglandins responsible for uterine contractions. Progesterone also limits the release of matrix metalloproteinases that can cause cervical effacement and softening by inhibiting the expression of contraction-associated protein genes (ion channels, oxytocin and prostaglandin receptors, and gap junctions) within the myometrium.
Although levels of progesterone in the maternal circulation do not change significantly in the weeks preceding labour, the onset of labour at term and preterm is associated with a functional withdrawal of progesterone activity at the level of the uterus.

Clinical efficacy/safety studies

A meta-analysis of individual participant data from randomised controlled trials (EPPPIC 2021) concluded that vaginal progesterone reduced birth before 34 weeks' gestation in high-risk singleton pregnancies. Trials in singleton pregnancies included mostly women with previous spontaneous preterm birth or short cervix. Preterm birth before 34 weeks was reduced in such women who received vaginal progesterone (nine trials, 3769 women; relative risk [RR] 0·78, 95% CI 0·68–0·90). Given increased underlying risk, absolute risk reduction was greater for women with a short cervix, hence treatment might be most useful for these women. Shared decision making with woman with high-risk singleton pregnancies should discuss an individual's risk, potential benefits, harms and practicalities of intervention. Treatment of unselected multifetal pregnancies with a progestogen was not supported by the evidence.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of different dosage (e.g. 300 mg vs. 600 mg) of progesterone administered into the vagina is non-linear. Systemic progesterone concentrations are the same with different dosages, because of local pharmacokinetic processes, such as direct passive diffusion or transport through the local blood circulation or lymph circulation, due to which progesterone will be transported from the vagina to the womb.

Absorption

Micronised progesterone administered in the vagina will be absorbed quickly and stable concentrations in plasma (4 – 12 ng/ml depending on the daily dosage) and average C_{max} at around the 8 hour mark is achieved with less individual fluctuation compared to orally taken medicine.

With a 600 mg daily dose of progesterone administered into the vagina the progesterone concentration in plasma were stable throughout administration times so that the highest average concentration was 11.63 ng/ml.

Distribution

Micronised progesterone administered into the vagina undergoes the first metabolic cycle in the womb, when progesterone distributes primarily or selectively into the womb, causing higher hormone levels in the womb and nearby tissues.

Progesterone is transported via the lymph and blood vessels and approximately 96%-99% is bound to serum proteins, primarily to serum albumin (50%-54%) and transcortin (43%-48%).

Elimination

By administering progesterone into the vagina, the first pass metabolism in the liver can be avoided, which enables concentrations in plasma to remain higher for longer.

95% of progesterone is eliminated from the urine as glycurone conjugated metabolites, mainly as 3 α, 5 β–pregnanediol (pregnandiol).

Biotransformation

Progesterone is metabolised by the liver.

Oral progesterone is excreted via the gallbladder and kidneys, with a half-life of 5 - 95 minutes. It is detectable in urine after 24 hours, and a small amount (8 - 17%) is secreted in the faeces.

After vaginal administration, observable levels of pregnanolone and 5α- dihydroprogesterone are very low, due to the lack of first-pass metabolism.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology and toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Sunflower oil, refined
Soybean lecithin

Capsule shell:
Gelatin Glycerol
Titanium dioxide (E171)
Water, purified

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The product is supplied in PVC/Aluminium blisters contained in cartons.
Pack sizes: Blister pack containing 15, 21, 45 or 90 capsules.
Not all pack sizes may be marketed

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 MARKETING AUTHORISATION HOLDER

Besins Healthcare Ireland Limited
Plaza 4, Level 4

Custom House Plaza
Harbourmaster Place
I.F.S.C.
Dublin 1 D01 A9N3
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22624/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th June 2019
Date of last renewal: 25th March 2024

10 DATE OF REVISION OF THE TEXT

August 2025