Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Utrogestan Vaginal 300 mg Vaginal Capsules, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 300 mg progesterone (micronized).

Excipient(s) with known effect: one capsule contains 3 mg of soya lecithin.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Vaginal capsule, soft
Oblong yellowish, soft gelatin capsule (approximately 2.5 cm x 0.8 cm) containing a whitish oily suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Utrogestan Vaginal is indicated in adult women for supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles.

4.2 Posology and method of administration

Posology
Vaginal use only.
The recommended dose is 600 mg/day, given in two divided doses, one in the morning and the other at bedtime. The treatment is started not later than the third day after oocyte retrieval day and is continued until at least the 7th week of pregnancy and not later than the 12th week of pregnancy or until menstruation begins.

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.

Method of administration
Vaginal
Each Utrogestan Vaginal capsule must be inserted deep into the vagina.
One capsule should be inserted deep into the vagina in the morning and the other at bedtime.

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 diseases
- Cerebral haemorrhage
- Porphyria
- Missed abortion
- Allergy to nuts or soya (see Section 4.4)

4.4 Special warnings and precautions for use

Warnings:

A complete medical examination must be performed before starting the treatment and regularly during the treatment.
Utrogestan Vaginal should only be used during the first three months of pregnancy and must only be administered by the vaginal route.
Utrogestan Vaginal is not suitable as a contraceptive.
Utrogestan Vaginal is not intended to treat an imminent premature delivery.
The use of micronised progesterone during the second and third trimester of pregnancy may lead to the development of gravidic cholestasis or hepatocellular liver disease.
Glucose tolerance may be impaired during progesterone treatment, and more frequent monitoring should be performed.
Progesterone has been linked to an increase in Type 2 diabetes, and adjustments in the medication of diabetes-treated patients may be required.
Treatment should be discontinued upon diagnosis of a missed abortion.

Precautions:

Any vaginal bleeding should always be investigated.
Utrogestan Vaginal contains soybean 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 4.4).

4.5 Interaction with other medicinal products and other forms of interaction

Progestagens may affect the treatment balance of diabetes and have been linked to an increase in Type 2 diabetes. The diabetes medicine of patients being treated simultaneously with progestagens may need to be adjusted.
Effects which progesterone may have on other medicines:
Progesterone may:

- Enhance or weaken the coagulating effect of coumarins and prevent the coagulating effect of phenindione
- Prevent the metabolism of ciclosporin, which increases the concentration of ciclosporin in plasma and the risk of toxicity
- Increase the concentration of tizanidine in plasma
- Interfere with the effect of bromocriptine

- Enhance the arrhythmogenicity of bupivacaine
- Alter the results of liver and/or endocrine function tests
- Prevent the oxidation of some benzodiazepine derivatives such as diazepam, chlordiazepoxide and alprazolam and to induce glucuronidation of oxazepam and lorazepam. These synergistic effects are probably not clinically significant, because the therapeutic spectrum of benzodiazepines are wide.

Interaction of other medicines on progesterone

The following medicines may increase the metabolism of progesterone:

- Perampanel or topiramate
- Some antibiotics, such as ampicillin, amoxicillin and tetracyclines may lower the concentration of steroids in plasma, because these antibiotics can have an effect on the hydrolysis of steroid conjugates in the bowel and on the reabsorption of non-conjugated steroid, in which case the concentration of the active steroid in the bowel will be reduced.
- Rifampicin and rifabutin

- Epilepsy medicines (not valproic acid): phenytoin, phenobarbital, carbamazepine, eslicarbazepine, oxcarbazepine, and primidone/rufinamide (by inducing oxidative decomposition)
- Herbal medicinal products, which contain St John's wort
- Antiretroviral medicines (protease blockers): darunavir, nelfinavir, fosamprenavir, lopinavir
- Bosentan
- Aprepitant.

The following medicines may prevent the metabolism of progesterone, which will lead to an increase in the bioavailability of progesterone:

- Fungal medicines (fluconazole, itraconazole, ketoconazole, voriconazole)
- Immunosuppressants (tacrolimus)
- Statins (atorvastatin, rosuvastatin)
- Monoamine oxidase (MAO) inhibiters (selegiline).

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.

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

Breast-feeding
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 subfertile or infertile women, there is no deleterious known effect on fertility.

4.7 Effects on ability to drive and use machines

Utrogestan Vaginal has no 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 below is based on experience gathered after the authorisation of progesterone administered into the vagina.
The following frequency conventions are used in the rating of undesirable effects: Very common (≥1/10); Common (≥1/100 to < 1/10); Uncommon (≥1/1000 to < 1/100); Rare (≥1/10000 to < 1/1000); Very rare (< 1/10000); Not known (cannot be estimated from the available data).

System Organ Class (SOC)	**Frequency very rare (<1/10000)**	**Frequency Not known (Cannot be estimated from the available data)**
Immune system disorders	Anaphylactic reactions	
Skin and subcutaneous tissue disorders		Pruritus
Reproductive system and breast disorders		Vaginal haemorrhage Vaginal discharge

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

Progesterone is a natural endogenous hormone of the corpus luteum and is the 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 has a gestagenic, antiestrogenic, slightly anti-androgenic and antialdosterone effects.

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

In clinical studies with a 300 mg dose of progesterone administered into the vagina daily for seven days the progesterone concentrations in plasma were stable throughout the administration times so that the average concentration was constantly over 6 ng/ml and average concentration was 8.03 ng/ml.

With a 600 mg daily dose of progesterone administered into the vagina the progesterone concentration in plasma were also stable throughout administration times so that the highest average concentration was 11.63 ng/ml. Likewise C_{max} was higher with 600 mg/day dosing compared to 300 mg/day.

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, mainly into 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 glucorone conjugated metabolites, mainly as 3 α, 5 β -pregnanediol (pregnanediol).

Biotransformation

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 pregnenolone and 5α-dihydroprogesterone are very low due to the lack of first-pass metabolism.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content of capsule:

- Sunflower oil, refined
- Soyabean lecithin

Capsule shell:

- Gelatin
- Glycerol (E422)
- Titanium Dioxide (E171)
- Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After opening: 15 days. Store below 30°C.

6.4 Special precautions for storage

Store below 30°C.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Utrogestan Vaginal capsule, soft, is packed in cartons containing:
White HDPE bottles of 15 capsules, with a white Polypropylene (PP) child-resistant screw cap and a tearable silver coloured seal.
PVC/Aluminium blisters containing 15, 30 or 45 capsules.
Not all pack sizes may be marketed

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 Healthcare Ireland Limited
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Dublin 1 D01 A9N3
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8 MARKETING AUTHORISATION NUMBER

PA22624/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st May 2021
Date of last renewal: 15th April 2025

10 DATE OF REVISION OF THE TEXT

October 2025