# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Utrogestan Vaginal 400 mg soft vaginal capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 400 mg progesterone.
Excipient(s) with known effect: soyabean lecithin.
For the full list of excipients, see Section 6.1.

## 3 PHARMACEUTICAL FORM

Soft vaginal capsules.
Oblong yellowish, soft capsule (approximately 2.5 cm x 0.9 cm) containing a whitish oily suspension.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Utrogestan 400 mg is indicated for the prevention of miscarriage in women presenting with bleeding in the first trimester of pregnancy and have a history of recurrent miscarriages (see sections 4.2 and 5.1).

### 4.2 Posology and method of administration

Treatment should always be individualised to the patient. The decision to treat women who have experienced recurrent miscarriages should follow further investigation and is at the discretion of the clinician.
Posology
**Vaginal use only.**
The recommended dose is 400 mg twice a day (morning and night). Treatment should be initiated during the first trimester of pregnancy, at first sign of vaginal bleeding (see Section 4.4 Special Warnings and Precautions for Use) and should continue to the 16th week of gestation.

*Paediatric population*
There is no relevant use of Utrogestan 400 mg in the paediatric population.
*Elderly patients*
There is no relevant use of Utrogestan 400 mg in the elderly.

Method of administration
Vaginal
Each Utrogestan 400 mg capsule 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
- 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 400 mg should only be used for threatened miscarriage during the first trimester; up to the 16th week of pregnancy and must only be administered by the vaginal route.
Utrogestan 400 mg is not suitable as a contraceptive.
Treatment should be discontinued upon diagnosis of a missed abortion.
***Precautions:***
Any vaginal bleeding should always be investigated.
**Utrogestan 400 mgcontains 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 400 mg (see Section 4.3).

**4.5 Interaction with other medicinal products and other forms of interaction**

Utrogestan 400 mg may interfere with the effects of bromocriptine and may raise the plasma concentration of ciclosporin. Utrogestan 400 mg may affect the results of laboratory tests of hepatic and/or endocrine functions.

Metabolism of Utrogestan 400 mg 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 malformation.
***Breast-feeding***
Utrogestan 400 mg is not indicated during breast-feeding. Detectable amounts of progesterone enter the breast milk.
***Fertility***
As this medicinal product is indicated to prevent miscarriage in women, there is no known deleterious effect on fertility.

**4.7 Effects on ability to drive and use machines**

Utrogestan 400 mg can have a moderate influence on the ability to drive and use machines.

**4.8 Undesirable effects**

Local intolerance (burning, itching or oily discharge) has been observed, but the incidence is extremely rare.
When used as recommended, transient fatigue or dizziness may occur within 1 – 3 hours of taking the medicine.
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 Not known (Cannot be estimated from the available data)** |
|---|---|
| Skin and subcutaneous tissue disorders | Pruritus |
| Reproductive system and breast disorders | Vaginal discharge<br>Vaginal haemorrhage |
| General disorders and administrative site conditions | Burning sensation |

**Reporting of suspected adverse reactions**
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 400 mg has 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.

The pharmacodynamic effects for threatened and recurrent miscarriage are that progesterone modulates maternal immune responses to protect the foetus, improves the utero-placental circulation, maintains cervical integrity throughout pregnancy, promotes myometrial relaxation, inhibits prostaglandin production, and possesses anti-inflammatory properties.

***Clinical efficacy/safety studies***

The efficacy and safety of micronized progesterone in preventing miscarriage in women, with dual risk factors of early pregnancy bleeding and previous history of miscarriages, was evaluated in the PRISM study. The benefit of treatment with vaginal progesterone 400 mg twice daily increased with an increasing number of prior miscarriages. The benefit reached statistical significance in the prespecified subgroup of women with three or more previous miscarriages and current pregnancy bleeding; live birth rate was 72% (98/137) with progesterone vs 57% (85/148) with placebo (rate difference 15%; risk ratio, 1.28, 95% CI, 1.08-1.51; P=.004). For this group, the number needed to treat was 8 (95% CI, 7-10). From a safety perspective, progesterone 400 mg was well tolerated.

**5.2 Pharmacokinetic properties**

Utrogestan 400 mg provides a local effect on the vagina and uterus. The efficacy of vaginal progesterone is related to the overall amount of progesterone accumulating in the endometrium and not to the amount that is systemically absorbed.

***Absorption***

Micronised progesterone is rapidly absorbed following vaginal administration. Unlike oral progesterone, vaginal progesterone does not undergo first pass metabolism in the gastrointestinal tract and liver. As a result of the "uterine first pass effect", relatively high concentrations occur in uterine and nearby tissues with low systemic exposure to progesterone and its metabolites.

The plasma exposure following administration of different vaginal dosages (e.g. 200 mg to 600 mg) is non-linear and increase less than proportional to dose. In a reported clinical study, administration of an 600 mg daily vaginal dose of progesterone resulted in stable plasma concentrations throughout administration times with the highest average plasma concentration equal to around 11.6 ng/ml.

***Distribution***

Vaginally accumulated progesterone undergoes the first metabolic cycle in the uterus, causing higher hormone levels in the uterus and nearby tissues.

The small amount of progesterone that is absorbed 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%).

***Biotransformation***

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

***Elimination***

95% of systemically absorbed progesterone is eliminated from the urine as glucorone conjugated metabolites.

**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.

**6.4 Special precautions for storage**

Store in the original packaging (the bottle).

**6.5 Nature and contents of container**

Utrogestan 400 mg, is packed in white HDPE bottles of 15 capsules, with a white Polypropylene (PP) child-resistant screw cap and a tearable silver coloured seal. The bottle is supplied in a cardboard carton.

**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
16 Pembroke Street Upper
Dublin 2
D02HE63
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA22624/001/004

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 22nd November 2024

**10 DATE OF REVISION OF THE TEXT**