SUMMARY OF PRODUCT CHARACTERISTICS

1. PRODUCT NAME

Utrogestan Vaginal 300 mg softgels

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 300 mg progesterone (micronized).
Notable excipient(s): each capsule contains 3 mg of soy lecithin
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft vaginal capsules.
Soft, yellowish, oblong gelatin capsule (approx. 2.5 cm x 0.8 cm) containing a whitish oily suspension.

4. CLINICAL DATA

4.1 Therapeutic indications

Utrogestan Vaginal is indicated for luteal phase supplementation as part of a medically assisted reproduction (MAP) program in adult women.

4.2 Dosage and administration

Dosage

Vaginal route only

The recommended dosage is 600 mg/day, in two doses, one in the morning and the other in the evening at bedtime. Treatment begins no later than the third day after the day of oocyte retrieval and continues at least until the 7th week of pregnancy and no later than the 12th week of pregnancy, or until the onset of menses.
Pediatric population
The use of Utrogestan Vaginal is not justified in the paediatric population.
Elderly patients
The use of Utrogestan Vaginal is not justified in the elderly.

Method of administration

Vaginal
Each Utrogestan Vaginal capsule should be inserted deep into the vagina.
Insert one capsule deep into the vagina in the morning and the other at bedtime.

4.3 Contra-indications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Jaundice

• Severe hepatic impairment
• Undiagnosed genital bleeding
• Carcinoma of the mammary or genital tract
• Thrombophlebitis
• Thromboembolic diseases
• Cerebral hemorrhage
• Porphyria
• Unsuccessful abortion
• Allergy to nuts or soy (see section 4.4)

4.4 Special Warning and precautions for use

Warnings :

A full medical examination should be carried out before starting treatment and regularly during treatment.
The use of Utrogestan Vaginal during pregnancy is reserved for the first trimester and by the vaginal route only.
Utrogestan Vaginal is not suitable as a contraceptive.
Utrogestan Vaginal is not intended for the treatment of imminent premature delivery.
The use of micronized progesterone during the second and third trimesters of pregnancy may lead to the development of gestational cholestasis or hepatocellular disease.
Glucose tolerance may be impaired during progesterone therapy, and more frequent monitoring is required. Progesterone has been associated with an increase in type
Type 2 diabetes, and medication adjustments may be necessary in patients being treated for diabetes.
Treatment should be discontinued as soon as a missed abortion is diagnosed.

Précautions

Any vaginal bleeding should always be investigated.
Utrogestan Vaginal contains soy lecithin and may cause hypersensitivity reactions (urticaria, anaphylactic shock in hypersensitive patients). As there is a possible relationship between soy allergy and peanut allergy, patients with peanut allergy should avoid using Utrogestan Vaginal (see section 4.3).

4.5 Interaction with other drugs and other forms of interaction

Progestins can affect the balance of diabetes treatment and have been associated with an increase in type 2 diabetes. Diabetes medication in patients treated simultaneously with progestins may need to be adjusted (see section 4.4).

Effects of progesterone on other drugs:

Progesterone may:

- Enhance or weaken the coagulant effect of coumarins and prevent the coagulant effect of phenindione
- Prevent the metabolism of cyclosporine, thus increasing the concentration of cyclosporine in plasma and the risk of toxicity.
- Increase plasma tizanidine concentration
- Interferes with the effect of bromocriptine
- Enhance the arrhythmogenicity of bupivacaine

• Alter liver and/or endocrine function test results
• Prevent oxidation of certain benzodiazepine derivatives such as diazepam, chlordiazepoxide and alprazolam, and induce glucuronidation of oxazepam and lorazepam. These synergistic effects are probably not clinically significant, as the therapeutic spectrum of benzodiazepines is broad.

Interaction of other drugs with progesterone

The following drugs may increase progesterone metabolism:

• Perampanel or topiramate
• Certain antibiotics, such as ampicillins, amoxicillin and tetracyclines, may lower the concentration of steroids in plasma, as these antibiotics may affect the hydrolysis of steroid conjugates in the intestine and the reabsorption of unconjugated steroids, in which case the concentration of the active steroid in the intestine will be reduced.
• Rifampicin and rifabutin
• Epilepsy drugs (not valproic acid): phenytoin, phenobarbital, carbamazepine, eslicarbazepine, oxcarbazepine and primidone/rufinamide (by inducing oxidative decomposition)
• Herbal medicines containing St. John's wort
• Antiretroviral drugs (protease inhibitors): darunavir, nelfinavir, fosamprenavir, lopinavir
• Bosentan
• Aprepitant.
The following drugs may inhibit progesterone metabolism, resulting in increased progesterone bioavailability:
• Fungal drugs (fluconazole, itraconazole, ketoconazole, voriconazole)
• Immunosuppressants (tacrolimus)
• Statins (atorvastatin, rosuvastatin)
• Monoamine oxidase (MAO) inhibitors (selegiline).

4.6 Fertility, Pregnancy and Breastfeeding
Natural progesterone can be administered orally, vaginally or intramuscularly to treat luteal phase deficiency up to at least 7 weeks' gestation and no later than 12 weeks' gestation.

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

Breast feeding
Utrogestan Vaginal is not indicated for use during breast-feeding. Detectable amounts of progesterone enter breast milk.

Fertility
As this drug is indicated to support luteal deficiency in hypofertile or infertile women, there is no known deleterious effect on fertility.

4.7 Effects on ability to drive and use machines
Utrogestan Vaginal has no effect on the ability to drive vehicles and use machines.

4.8 Undesirable Effects
Local intolerance (burning, itching or oily discharge) has been observed in clinical studies and reported in publications, but the incidence is extremely rare.

When used as recommended, transient fatigue or dizziness may occur within 1 to 3 hours.
Reporting suspected adverse reactions after authorization.
The information below is based on post-marketing experience with vaginally administered progesterone.

The adverse reactions listed below are classified according to their frequency of occurrence: 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); Frequency undetermined (cannot be estimated on the basis of available data).

Organ class systems	**Very rare (< 1/10,000)**	**Undetermined frequency** **(cannot be estimated on the basis of available data)**
Immune system disorders	Réaction anaphylactique	
Skin and subcutaneous tissue disorders		Pruritus
Reproductive organs and breast disorders		Vaginal hemorrhage Vaginal discharge

Reporting suspected adverse reactions

Reporting suspected adverse reactions after a drug has been authorized is important. It enables ongoing monitoring of the drug's risk/benefit ratio. Healthcare professionals report all suspected adverse reactions via the national reporting system:

http://agp.com.pk/adverse-event-form/

You can also report side effects to DRAP through MED Vigilance E-Reporting system of DRAP available online at : https://primaryreporting.who-umc.org/pk.

4.9 Overdosing
Symptoms of overdose may include drowsiness, dizziness, euphoria or dysmenorrhea. Treatment is observation and, if necessary, symptomatic and supportive measures should be taken.

5. Pharmacological Properties
5.1 Pharmacodynamic Properties
Pharmacotherapeutic class: sex hormones and genital system modulators, progestins, 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 placenta. It acts on the endometrium by converting the proliferative phase into the secretory phase. Utrogestan Vaginal has all the properties of endogenous progesterone with induction of a complete secretory endometrium, and in particular has a gestagenic, antiestrogenic, slightly anti-androgenic and anti-aldosterone effect.

5.2 Pharmacokinetic Properties

The pharmacokinetic profile of different doses (e.g. 300 mg vs. 600 mg) of progesterone administered vaginally is not linear. Systemic progesterone concentrations are the same at different dosages, due to local pharmacokinetic processes, such as direct passive diffusion or transport through the local bloodstream or lymphatic circulation, by which progesterone will be transported from the vagina to the uterus.

Absorption

Micronized progesterone administered vaginally will be absorbed rapidly and stable concentrations in plasma (4-12 ng / ml depending on daily dosage) and mean Cmax at around 8 hours is achieved with less individual fluctuation compared to the drug taken orally..

In clinical studies with a 300 mg dose of progesterone administered daily into the vagina for seven days, plasma progesterone concentrations were stable throughout the administration times, so that the mean concentration was consistently above 6 ng / ml and the mean concentration was 8.03 ng / ml. With a daily dose of 600 mg progesterone administered vaginally, the concentration of progesterone in plasma was also stable throughout the administration time, so that the highest mean concentration was 11.63 ng / ml. Similarly, Cmax was higher with a dose of 600 mg / day compared with 300 mg / day.

Distribution

Micronized progesterone administered into the vagina undergoes the first metabolic cycle in the uterus, when progesterone distributes predominantly or selectively in the uterus, resulting in higher hormone levels in the uterus and surrounding tissues.

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

Elimination

By administering progesterone vaginally, first-pass metabolism in the liver can be avoided, allowing plasma concentrations 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 the 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 absence of first-pass metabolism.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL DATA

6.1 List of excipients
Capsule content:
• Sunflower oil
• Soya lecithin

Capsule shell:
• Gelatin
• Glycerol (E422)
• Titanium Dioxide (E171)
• Purified Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Three years.
After opening: 15 days. Store at temperatures not exceeding 30°C.

6.4 Special storage precautions
Store at a temperature not exceeding 30°C.
For storage conditions after first opening, see section 6.3.

6.5 Nature and contents of packaging
Utrogestan Vaginal softgels are supplied in white high-density polyethylene (HDPE) plastic bottles containing 15 capsules, fitted with a child-resistant white polypropylene (PP) screw cap and a silver tear-off seal.

6.6 Special disposal precautions
Any unused medicine or waste must be disposed of in accordance with current regulations.

7 REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER:

Marketing Authorization Holder in Belgium
Besins Healthcare S.A.,
Rue Washington 80, 1050
Ixelles, Belgium.

Marketing Authorization Holder in Pakistan
M/s AGP Limited
Address: B-23-C, S.I.T.E., Karachi
Fax: +9221 32570678
E-mail: info@agp.com.pk

Manufacturer

Name of Manufacturing Site	Address of Site	Manufacturing Step (If applicable)

Cyndea Pharma, S.L.	Poligono Industrial Emiliano Revilla Sanz, Avenida de Agreda, 31, Olvega 421 10 (Soria) Spain.	-

8 REGISTRATION / MARKETING AUTHORIZATION NUMBER
122460

9 DATE FROM WHICH MARKETING IS AUTHORIZED:

Date of first authorization: 11th October, 2024

10 TEXT UPDATE DATE

Not Applicable