SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Utrogestan Vaginal 200mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 200 mg micronised progesterone.
Excipients with known effect: Soya lecithin
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Vaginal Capsules, soft
White

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.

4.2 Posology and method of administration

Posology
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.

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.

4.3 Contraindications

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

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 administered by vaginal route. Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.

Utrogestan Vaginal 200mg Capsules are not suitable
• in the treatment of premature labour, or
• in threatened abortion, or
• 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).

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 (IC\textsubscript{50} < 0.1 \(\mu\)M). 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 subfertile or infertile women, there is no deleterious known effect on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Local intolerance (burning, pruritus or fatty discharge) has been observed during the different clinical trials and reported in the literature but incidences were extremely low.

No systemic side effects, in particular somnolence or dizziness (observed with the oral form), have been reported during clinical studies at the recommended dosages.

**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 the website www.mhra.gov.uk/yellowcard.
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 (ATC code: G03DA): Progestagens

Mechanism of action

Progesterone is a natural progestogen, the main hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase. Utrogestan Vaginal 200mg Capsules 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.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, micronised progesterone is absorbed by the digestive tract. Pharmacokinetic studies conducted in healthy volunteers have shown that after oral administration of two 100 mg capsules (200mg), plasma progesterone levels increased to reach the Cmax of 13.8ng/ml +/- 2.9ng/ml in 2.2 +/- 1.4 hours. The elimination half-life observed was 16.8 +/- 2.3 hours.

Although there were inter-individual variations, the individual pharmacokinetic characteristics were maintained over several months, indicating predictable responses to the drug.

Following vaginal administration, micronised progesterone is absorbed rapidly and achieves stable plasma levels in the range of 4-12 ng/ml, depending on the daily dose, with much less inter-subject variation than following oral administration.

Distribution
Progesterone is approximately 96%-99% bound to serum proteins, primarily to serum albumin (50%-54%) and transcortin (43%-48%).

Elimination
Urinary elimination is observed for 95% in the form of glycuropregnaded conjugated metabolites, mainly 3a, 5b-pregnanediol (pregnandiol).
Biotransformation

Progesterone is metabolised primarily by the liver. Following oral administration, the main plasma metabolites are 20α-hydroxy-Δ4 α-prenolone and 5α-dihydroprogesterone. Some progesterone metabolites are excreted in the bile and these may be deconjugated and further metabolised in the gut via reduction, dehydroxylation and epimerisation. The main plasma and urinary metabolites are similar to those found during the physiological secretion of the corpus luteum.

Following vaginal administration, only low plasma levels of pregnanolone and 5α-dihydroprogesterone are detected, 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.

Utrogestan Vaginal 200mg Capsules

1. Name of the medicinal product
UTROGESTAN VAGINAL 200MG CAPSULES

2. Qualitative and quantitative composition
Each capsule contains 200 mg micronised progesterone.
Excipients with known effect: Soya lecithin
For a full list of excipients, see Section 6.1.

3. Pharmaceutical form
Vaginal Capsules, soft
White

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6. Pharmaceutical particulars
6.1 List of excipients
- Sunflower oil, refined
- Soya lecithin
- Gelatin
- Glycerol
- Titanium dioxide
- Purified water

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special precautions for storage.

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 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
Avenue Louise, 287
B-1050 Brussels
Belgium

8. Marketing authorisation numbers
PL 28397/0005

9. Date of first authorisation/renewal of the authorization
21/12/2012

10. Date of revision of the text

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Avenue Louise, 287
B-1050 Brussels
Belgium

8 MARKETING AUTHORISATION NUMBER(S)
PL 28397/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
21/12/2012

10 DATE OF REVISION OF THE TEXT
29/06/2017