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 administrated 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_{50} <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 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 glycuroconjugated metabolites, mainly 3 α, 5 β–pregnanediol (pregnandiol).

Biotransformation

Progesterone is metabolised primarily by the liver.

Following oral administration, the main plasma metabolites are 20 α hydroxy- Δ 4 α- prenolone and 5 α-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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sunflower oil, refined
Soya lecithin
Gelatin
Glycerol
Titanium dioxide

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

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 NUMBER(S)

PL 28397/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/12/2012

10 DATE OF REVISION OF THE TEXT

22/06/2015

SUMMARY OF PRODUCT CHARACTERISTICS

UTROGESTAN VAGINAL soft capsules

1. NAME OF THE MEDICINAL PRODUCT

Utrogestan Vaginal 100 mg Soft capsules
Utrogestan Vaginal 200 mg Soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Utrogestan Vaginal 100 mg: *100 mg progesterone (micronised).*
Utrogestan Vaginal 200 mg: *200 mg progesterone (micronised).*

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal soft capsules.

Utrogestan Vaginal 100 mg: Spherical, off-white capsules.
Utrogestan Vaginal 200 mg: Oval, off-white capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Subfertility or primary/secondary infertility due to partial or total luteal phase deficiency (in particular: poor ovulation, supplementation of the luteal phase during *in vitro* fertilisation, egg donations).

- Threat of miscarriage or prevention of recurrent miscarriages due to luteal phase deficiency.

4.2 Posology and method of administration

Posology

On average, the dosage is 200 mg progesterone per day (i.e. one 200 mg capsule or two 100 mg capsules spread over two doses, one in the morning and one in the evening), to be inserted deep into the vagina, possibly with the aid of an applicator. This can be increased depending on the patient's response.

- For **luteal phase deficiency** (poor ovulation, menstrual irregularities): the treatment is used for 10 days per cycle, usually from **days 17 to 26** inclusive, at a rate of 200 mg progesterone per day.
- In cases of **infertility with total luteal phase deficiency (egg donations)**: the progesterone dose is 100 mg progesterone on days 13 and 14 of the transfer cycle, then 100 mg progesterone on the morning and evening of days 15 to 25 of the cycle. From day 26 onwards, the dose is increased - in the event of conception - by 100 mg progesterone per day each week, reaching a maximum of 600 mg progesterone per day, spread over three doses. This dosage is maintained up until day 60.
- For **luteal phase supplementation during IVF**: treatment is initiated starting from the evening of the transfer, at a rate of 600 mg progesterone spread over three doses: morning, noon and evening.
- For **threatened miscarriages or in the prevention of recurrent miscarriages due to luteal phase deficiency**: the average dosage is 200 mg to 400 mg progesterone per day, spread over two doses, up until week 12 of pregnancy.

Method of administration

Vaginal administration: the capsules must be inserted deep inside the vagina.

4.3 Contraindications

This medicinal product must not be prescribed in the following situations:

- serious changes in liver function.
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- neoplasm of the breast or genital organs, suspected or confirmed.

4.4 Special warnings and precautions for use

This treatment, under the recommended conditions of use, **IS NOT CONTRACEPTIVE**.
If the treatment schedule is initiated too early in the month, particularly before day 15 of the cycle, this may shorten the cycle and/or bleeding may occur.
The woman must insert each capsule deep into the vagina.

- In the case of uterine bleeding, do not prescribe until a definite cause has been established, preferably via endometrial investigation.
- Due to the thromboembolic and metabolic risks which cannot totally be eliminated, treatment must be discontinued at the onset of:
  - eye disorders, such as loss of vision, diplopia, vascular lesions of the retina;
  - venous thromboembolisms or thrombotic events, regardless of the region;
  - severe headaches.
- Patients with a history of thrombophlebitis should be closely monitored.
- If amenorrhoea should occur during treatment, pregnancy must be excluded.

More than half of spontaneous abortions are due to genetic complications. Furthermore, infectious manifestations and mechanical disorders may be responsible

for miscarriages; in which case, the sole effect of administering progesterone would be a delay in the expulsion of a dead ovum. Progesterone administration must therefore only be reserved for cases where corpus luteum secretion is insufficient.

Utrogestan Vaginal contains soya lecithin and may cause hypersensitivity reactions (urticaria, anaphylactic shock).

4.5 Interaction with other medicinal products and other forms of interaction

Combination with other medicinal products may reduce the metabolism of progesterone, which may lead to a modification in its effect.

This applies in the case of:
- potent enzyme inducers such as barbiturates, antiepileptic agents (phenytoin), rifampicin, phenylbutazone, spironolactone and griseofulvin. These medicines cause increased metabolism in the liver.
- certain antibiotics (ampicillin, tetracyclines): variations in the intestinal flora, leading to a change in the enterohepatic circulation of steroids.

Since these interactions can differ depending on the individual, it is not always possible to predict clinical results.

Progestins may cause a reduction in glucose tolerance and, as a result, may increase the need for insulin and other antidiabetic agents in patients with diabetes.

Smoking may reduce the bioavailability of progesterone and alcohol abuse may increase it.

4.6 Fertility, pregnancy and lactation

The use of UTROGESTAN VAGINAL Soft capsules is not contraindicated during pregnancy, including the first few weeks (see section 4.1: Therapeutic indications - Obstetric).

The passage of progesterone into milk has not been studied in detail. Its prescription should therefore be avoided during the breastfeeding period.

4.7 Effects on ability to drive and use machines

Cases of drowsiness and dizziness have been reported with the oral route.

Attention should be drawn to the risks of drowsiness and/or dizziness associated with the oral use of this medicine, particularly in the case of patients who drive or operate machinery. Ingestion of the capsules at bedtime will avoid such problems.

4.8 Undesirable effects

Despite the possibility that local irritation may occur (soya lecithin), no significant local intolerance (burning, pruritus or greasy discharge) has been observed during various clinical studies.

The following effects have been reported with soft capsules administered **via the oral route**:

System organ class	Common undesirable effects ≥1/100; <1/10	Uncommon undesirable effects ≥1/1,000; ≤1/100	Rare undesirable effects ≥1/10,000; ≤1/1,000	Very rare undesirable effects ≤1/10,000
Reproductive system and breast disorders	. Altered menstrual cycles . Amenorrhoea . Intermenstrual bleeding	. Mastodynia		
Nervous system disorders	. Headache	. Drowsiness . Transient dizziness		. Depression
Gastrointestinal disorders		. Vomiting . Diarrhoea . Constipation	. Nausea	
Hepatobiliary disorders		. Cholestatic jaundice		
Immune system disorders				. Urticaria
Skin and subcutaneous tissue disorders		. Pruritus . Acne		. Chloasma

Drowsiness and/or transient dizziness are observed particularly with concomitantly low levels of oestrogen. These effects are immediately reversible upon reduction of the dosage or escalation of the oestrogen dose, without compromising the therapeutic benefit.

If the treatment schedule is initiated too early in the month, particularly before day 15 of the cycle, this may shorten the cycle or intermenstrual bleeding may occur.

Altered menstrual cycles, amenorrhoea and intermenstrual bleeding have been observed and reported in association with general progestin use.

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 national reporting system:

Belgium
Agence fédérale des médicaments et des produits de santé
(Federal Agency for Medicines and Health Products)
Division Vigilance
(Vigilance Department)
EUROSTATION II
Place Victor Horta, 40/ 40

B-1060 Brussels
Website: www.afmps.be
e-mail: adversedrugreactions@fagg-afmps.be

Luxembourg
Direction de la Santé – Division de la Pharmacie et des Médicaments
(Health Directorate - Pharmacy and Medicines Division)
Villa Louvigny – Allée Marconi
L-2120 Luxembourg
Website:
http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html

4.9 Overdose

Despite the fact that no overdose has been reported to date with the vaginal form, the undesirable effects described above could be signs of an overdose. They resolve spontaneously when the dosage is reduced.

In some individuals, the usual dosage may prove to be too high, as evidenced by the persistence or recurrence of unstable endogenous progesterone secretion, marked sensitivity to the product or concomitantly low blood levels of oestradiol. In these cases, the following measures should be taken:

- In the event of drowsiness or transient dizziness, the dosage amount should be reduced or progesterone should be administered IN THE EVENING AT BEDTIME, over 10 days per cycle.
- In the event of spotting/shortening of the menstrual cycle, initiation of treatment should be deferred until later into the cycle (e.g. day 19 instead of day 17).
- Perimenopausal women/women receiving HRT should be tested to ensure that blood oestradiol levels are sufficient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Genitourinary system and sex hormones
ATC code: G03DA04

Utrogestan Vaginal Soft capsules, containing progesterone in micronised form, allows a significant increase in plasma progesterone levels following vaginal administration, thus making it possible to correct progesterone deficiency.

5.2 Pharmacokinetic properties

Elevation of blood progesterone levels starts from the first hour onwards, with peak plasma levels observed 1 to 3 hours after administration.

At the average recommended dose, **stable** physiological levels of plasma progesterone, similar to those obtained during the luteal phase of a normal, ovulatory menstrual cycle, can be reached and maintained.

Thus, Utrogestan Vaginal Soft capsules induce adequate endometrial maturity, promoting the implantation of a potential embryo.
At higher doses, increased gradually, this route of administration makes it possible to achieve blood progesterone levels similar to those observed during the first trimester of pregnancy.

Metabolism: plasma and urinary metabolites are identical to those found during physiological corpus luteum secretion: in plasma, its main metabolites are 20-alpha-hydroxy-delta-4-pregnenolone and 5-alpha-dihydroprogesterone. Urinary elimination occurs at a rate of 95% in the form of glucuronide-conjugated metabolites, the main one being 3-alpha-5-beta pregnanediol (pregnandiol).

5.3 Preclinical safety data

No data supplied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents: sunflower oil, soya lecithin.
Capsule shell: gelatin, glycerol, titanium dioxide, purified water (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Three years in the sealed blister.

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions.
Store in the original package.

6.5 Nature and contents of container

Boxes of 30 or 90 x 100 mg soft capsules, packed in blisters, for vaginal use.
Boxes of 15 or 45 x 200 mg soft capsules, packed in blisters, for vaginal use.

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 MANUFACTURING BENELUX
Avenue Louise, 287

1050 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBERS

Utrogestan Vaginal 100 mg soft capsules: BE 178954
Utrogestan Vaginal 200 mg soft capsules: BE 279377

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation
100 mg: 22/10/1996
200 mg: 09/01/2006

Date of latest renewal
100 mg: February 2007

10. DATE OF REVISION OF THE TEXT

Last revised: Feb 2016
Date of approval by the Belgian Federal Agency for Medicines and Health Products: Feb 2016