1. NAME OF THE MEDICINAL PRODUCT

Utrogestan Vaginal 100 mg capsules, soft
Utrogestan Vaginal 200 mg capsules, soft

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Utrogestan Vaginal 100 mg capsules, soft: 100 mg progesterone (micronised)
Utrogestan Vaginal 200 mg capsules, soft: 200 mg progesterone (micronised)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft vaginal capsules

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Hypofertility or primary/secondary infertility due to partial or total luteal phase deficiency (in particular: dysovulation, supplementation of the luteal phase during in vitro fertilisation, oocyte donations).

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

4.2. Posology and method of administration

Vaginal administration: the capsules must be inserted at the back of the vagina.

The usual daily dosage is 200 mg of progesterone (i.e. one 200 mg capsule or two 100 mg capsules taken in two doses, one in the morning and one in the evening), to be inserted deep into the vagina, with or without the help of an applicator. This dosage may be increased depending on the individual patient response.
- In the case of **partial luteal phase deficiency** (poor ovulation, irregular menstrual cycles): the daily dose is 200 mg progesterone, administered over 10 days per menstrual cycle, usually from **cycle days 17 to 26**.

- In the case of **infertility associated with total luteal phase deficiency** (oocyte donations): the initial progesterone dose is 100 mg, administered on days 13 and 14 of the transfer cycle, followed by 100 mg of progesterone given in the morning and evening of cycle days 15 to 25. From day 26 onwards, in the event of conception, dosage is escalated in weekly increments of 100 mg progesterone per day, to reach a maximum daily dose of 600 mg progesterone, spread over three doses. This dosage is maintained up until day 60.

- In the case of **luteal phase supplementation during IFV**: treatment is initiated in the evening of the transfer, at a rate of 600 mg progesterone spread over three doses (morning, noon and evening).

- In the case of **threatened miscarriages or in the prevention of LPD-related recurrent spontaneous abortions**: the usual daily dosage is 200 mg to 400 mg progesterone, spread over two doses, to be taken up until gestation week 12.

### 4.3 Contraindications

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

- Severe changes in hepatic function.
- Known hypersensitivity to the active substance or any of the excipients.

### 4.4 Special warnings and precautions for use

The treatment, when administered in accordance with the recommended schedules, **IS NOT CONTRACEPTIVE**.

The menstrual cycle may be curtailed and/or bleeding may occur if the treatment sequence is initiated too early, particularly before cycle day 15.

Patients must insert each capsule at the back of the vagina.

- In the presence of uterine bleeding, Utrogestan must not be prescribed until a definite cause has been established, preferably via endometrial investigation.

- As it is impossible to achieve total elimination of thromboembolic and metabolic risks, treatment should be suspended at the onset of any:
  - eye disorders, such as loss of vision, diplopia, vascular lesions of the retina;
  - venous thromboembolisms or thrombotic events, regardless of the territory;
  - severe headaches.

- Patients with a history of thrombophlebitis should be closely monitored.

- If amenorrhoea should occur at any time during treatment, the patient should undergo a pregnancy test.

More than half of early spontaneous abortions (miscarriages) are caused by genetic complications. Furthermore, they may also be caused by infectious manifestations and mechanical disorders; in which case, the sole result of administrating progesterone would be to delay expulsion of a dead ovum. Progesterone administration must therefore only be reserved for cases where corpus luteum secretion is inadequate.

### 4.5 Interaction with other medicinal products and other forms of interaction
Co-administration with other drugs may increase the metabolism of progesterone, which may lead to a modification in its effect.

This applies in the case of:
- Powerful enzyme inducers such as barbiturates, antiepileptic agents (phenytoin), rifampicin, phenylbutazone, spironolactone and griseofulvin. These drugs enhance metabolism in the liver.
- Certain antibiotics (ampicillin, tetracyclines): variations in the intestinal flora, which lead to a change in the enterohepatic circulation of steroids.

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

Progestins may cause a reduction in glucose tolerance, which increases the need for insulin and other anti-diabetic agents in diabetic patients.

4.6 Pregnancy and lactation

The use of Utrogestan Vaginal capsules, soft is not contraindicated during pregnancy including the first few weeks (cf. section 4.1: Therapeutic indications).

No exact studies have been performed to establish whether progesterone passes into human milk. It should therefore not be prescribed to nursing mothers.

4.7 Effects on ability to drive and use machines

Drowsiness and dizziness have been reported in patients via the oral route.

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

4.8 Undesirable effects

Although local irritation may occur (due to the presence of soya lecithin), no local intolerance reactions (burning sensations, pruritus or greasy discharge) have been observed during the various clinical studies performed.

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

<table>
<thead>
<tr>
<th>System</th>
<th>Common undesirable effects &gt;1/100; &lt;1/10</th>
<th>Uncommon undesirable effects &gt;1/1000; &lt;1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive</td>
<td>. Altered menstrual cycles . Amenorrhoea . Intermenstrual bleeding</td>
<td></td>
</tr>
<tr>
<td>Nervous</td>
<td>. Headaches . Drowsiness . Transient dizziness</td>
<td></td>
</tr>
</tbody>
</table>
Drowsiness and/or transient dizziness are particularly observed in patients with concomitantly low levels of oestrogen. These effects are immediately reversible upon reduction of the Utrogestan dosage or escalation of the oestrogen dose, without compromising the therapeutic benefit.

The menstrual cycle may be curtailed and/or intermenstrual bleeding may occur, if the treatment sequence is initiated too early, particularly before cycle day 15.

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

4.9 Overdose

Despite the fact that no case of overdose has so far been reported with the vaginal form, the undesirable effects given above may be symptomatic of overdosage. A reduction in dosage will cause such signs to regress spontaneously.

In some users, the usual dosage may prove to be too high, as evidenced by the persistence or recurrence of uncontrolled endogenous progesterone secretion, marked sensitivity to the product itself or concomitantly low levels of blood oestradiol. The following measures should be taken:
- In the event of drowsiness or transient dizziness, the dosage amount should be titrated downwards. Alternatively, progesterone should be administered in the evening BEFORE RETIRING, over a 10-day period per cycle.
- In the event of breakthrough bleeding (spotting)/ curtailing 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 capsules, soft, which contain progesterone in micronised form, significantly increases plasma progesterone levels following vaginal administration thus making it possible to correct any deficits in progesterone.

5.2 Pharmacokinetic properties

Elevation of blood progesterone levels starts from the first hour onwards, with peak plasma levels reached within 1 – 3 hours following administration.

At the standard 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.
Utrogestan Vaginal capsules, soft induce adequate endometrial maturity, thus promoting embryo implantation.
At higher doses, reached via gradual upward titration, this route of administration makes it possible to achieve blood progesterone levels similar to those observed during the first trimester of pregnancy.

Metabolisation: plasma and urinary metabolites are identical to those found during physiological corpus luteum secretion. Its main plasma metabolites include 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. Its main urinary metabolite is 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, glycerin, titanium dioxide (E171)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years in its sealed blister strip.

6.4 Special precautions for storage
No special storage conditions
Store in the original package

6.5 Nature and contents of container
Each box contains 30 or 90 units of 100 mg soft capsules packed in blister strips, for vaginal administration.
Each box contains 15 or 45 units of 200 mg soft capsules packed in blister strips, for vaginal administration.

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 LANUF1ACTURING BELGIUM S.A.
Groot-Bijgaardenstraat 128
8. MARKETING AUTHORISATION NUMBERS

Utrogestan Vaginal 100 mg capsules molles: BE 178954
Utrogestan Vaginal 200 mg capsules molles: 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 authorisation renewal:
100 mg: February 2007

10. AVAILABILITY STATUS

On medical prescription only

11. DATE OF REVISION OF THE TEXT

Last revised in: December 2010
Date of approval by the Belgian Federal Public Service for Public Health: 12/2010