Summary of Product Characteristics

1. Name of Medicinal Product

Utrogestan 100 mg Soft Gel Capsule

2. Quality and Quantitative Composition

Each soft gel capsule contains:
Progesterone…… 100 mg

3. Pharmaceutical Form

Utrogestan 100 mg: Round slightly yellow capsule containing a whitish oily suspension.

4. Clinical Particulars

4.1 Therapeutic Indications By

4.2 oral route:

- Disorders associated with a progesterone defi cit: pre-menstrual syndrome, menstrual irregularity, benign breast disease, pre-menopause
- Treatment of the menopause (as an adjuvant to oestrogen therapy),
- Infertility caused by luteal phase defect.
- Menace of abortion or prevention of recurrent spontaneous abortions due to diagnosed luteal phase defect,
- Menace of preterm delivery.

By vaginal route:

- During In Vitro Fertilization cycles (IVF).
- Menace of abortion or prevention of recurrent spontaneous abortions due to luteal phase defect
- Menace of preterm delivery.

4.2 Posology and Method of Administration

Oral route

The standard daily dosage regimen is 200 to 300 mg of progesterone taken in one or two doses, i.e. 200 mg in the evening at bedtime and another 100 mg in the morning, if needed.

In the case of luteal phase defect (pre-menstrual syndrome, menstrual irregularity, pre- menopause, benign breast disease, the treatment is administered over 10 days per menstrual cycle, usually from cycle days 17 to 26 inclusive.

In the treatment of the menopause given that stand-alone oestrogen therapy is not recommended, progesterone may be used as an adjuvant, to be given during the last two weeks of the treatment sequence, followed by a one-week suspension of all replacement therapy, during which withdrawal bleeding may be observed.

In the case of threatened abortion 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.

In the case of threatened preterm delivery: 400 mg of progesterone every 6 to 8 hours, depending on the clinical

results obtained during the acute phase, followed by a maintenance dose (e.g. 3 x 200 mg a day) to be taken up until gestational week 36.

Vaginal route

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 defect (dysovulation, 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 defect (oocyte donation): 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 increased 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 IVF 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 abortion 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.

In the case of threatened preterm delivery: Active treatment: 200 mg – 300 mg × 2 – 3 times/day in 3 days. Maintain dosage: 100 mg – 200 mg/day until suppression of contraction.

4.3 Contraindications

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

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

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

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.

More than half of early spontaneous abortions (miscarriages) are caused by genetic disorders. 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.

During HRT involving oestrogens, administration of progesterone over a minimum of 12 days per cycle is strongly recommended.

4.5 Interaction with other medicinal products and other forms of interactions

Powerful enzyme inducers such as barbiturates, antiepileptic agents (phenytoin), rifampicin, phenylbutazone, spironolactone and griseofulvin. These drugs enhance metabolisation in the liver.

Certain antibiotics (ampicillin, tetracyclines): variations in the intestinal fl ora, which lead to a change in the enterohepatic circulation of steroids.

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

4.6 Fertility, pregnancy and breastfeeding

The use of Progesterone (Utrogestan) soft capsules is not contraindicated during pregnancy including the fi rst few weeks.
It should not be prescribed to nursing mothers.

4.7 Effects on ability to drive and use machines

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. Intake of capsules at bedtime will avoid such problems.

4.8 Undersirable effects

After vaginal administration, local irritation may occur (due to the presence of soya lecithin, sunflower oil).
The following effects have been reported in association with soft capsules administered via the oral route:
Common undesirable effects: altered menstrual cycles, amenorrhoea, intermenstrual bleeding, headaches.
Uncommon undesirable effects: drowsiness, transient dizziness, cholestatic jaundice, pruritus, gastrointestinal disorders.
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 shortened 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.

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 Overdose

With vaginal administration, no case of overdose has so far been reported. With oral administration, the undesirable effects described above are mostly 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:

Progesterone should be administered in the evening AT BEDTIME, over a 10-day period per cycle.

In the event of breakthrough bleeding (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 Pharmacologic properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Genitourinary system sex hormones ATC code: G03DA04
Progesterone (Utrogestan) which contains progesterone in micronized form, significantly increases plasma progesterone levels following oral and 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.

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).

Oral route: Owing to the tissue retention time of the hormone, it might be prudent to divide the dosage into two doses, to be taken at 12-hourly intervals approx., in order to ensure that impregnation is obtained throughout the entire 24-hour period.

Vaginal route: 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. Progesterone (Utrogestan)Vaginal soft capsules, 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.

5.3 Preclinical Safety Data Not supplied

6 Pharmaceutical Particulars

6.1 List of excipients

Capsule contents: sunflower oil, soya lecithin

Capsule shell: gelatin, glycerol titanium oxide, purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions

6.5 Nature and contents of container

Box of 30’s, 100 mg soft capsule, packed in blisters

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.,
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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
116847

9 DATE FROM WHICH MARKETING IS AUTHORIZED:

Date of first authorization: 5th May, 2023

10 TEXT UPDATE DATE

Not Applicable