FRONT

UTROGESTAN® 100 mg and 200 mg
Soft Capsules
Micronised Progesterone

COMPOSITION
Utrogestan for oral and vaginal use contains the following active ingredient: Progesterone (micronized) 100mg or 200mg. They also contain the following excipients: sunflower oil, soya lecithin and glycerol. Soya bean is known to have a recognized effect. The capsule contains gelatin, titanium dioxide (171).

DESCRIPTION
Utrogestan 100mg soft capsule is a around, slightly yellow, soft capsule containing a whitish oily suspension.
Utrogestan 200mg, soft capsule in an ovoid, slightly yellow, soft capsule containing a whitish oily suspension.

PHARMACOLOGY
ATC Code: G03DA04: Genito-urinary system and sex hormones

Pharmacodynamics
Progesterone is a naturally occurring steroid hormone that is secreted by the ovary, placenta and adrenal gland. It acts on the endometrium by converting the proliferating phase to the secretory phase. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo, and once an embryo is implanted, progesterone acts to maintain the pregnancy. As well as gestagenic actions, progesterone also has anti-estrogenic, slightly anti-androgenic and anti-aldosterone effects.

Pharmacokinetics
Absorption
Following oral administration, micronized 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, micronized 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
Following vaginal administration of micronized progesterone, relatively high concentrations of progesterone are found in the uterus and nearby tissues with correspondingly low systemic
exposure. Progesterone enters both the lymph system and the blood vessels, as outlined for the uterine first-pass effect. Progesterone is approximately 96-99% bound to serum proteins, primarily to serum albumin (50-54%) and transcortin (corticosteroid binding globulin) (43-48%).

Metabolism
Progesterone is metabolized primarily by the liver. Following oral administration, the main plasma metabolites are 20α hydroxy-Δ4α-prenolone and 5 α-dihydroprogesterone. Some progesterone metabolites are excreted in the bile and these may be deconjugated and further metabolized in the gut via reduction, dehydroxylation and epimerisation.
The main plasma and urinary metabolites are like 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.

Excretion
Urinary elimination is observed for 95% in the form of glycuroconjugated metabolites, mainly 3α, 5β–pregnanediol (pregnandiol).

INDICATION
Utrogestan is indicated for:
Disorders related to progesterone deficit in particular menstrual irregularities due to ovulation disorders or anovulation, premenstrual disorders, breast pain or by benign breast disorders (mastopathies), bleeding due to fibroma, therapy of menopause (adjunctive use with estrogen in post-menopausal women for prevention of endometrial hyperplasia, menace of preterm delivery and can be used up to 36 week of pregnancy, threatened miscarriage or prevention of habitual miscarriage due to luteal phase deficiency up to the 12th week of pregnancy, treatment of subfertility or primary or secondary infertility related to progesterone insufficiency in particular in In Vitro Fertilization) cycles and/or oocyte donation.
For all other progesterone indications, the vaginal route represents an alternative to the oral route, in case of adverse events due to Progesterone (somnolence, dizziness).

RECOMMENDED DOSAGE
On the average for progesterone deficiencies, the daily dose is 200mg to 300 mg divided into one or two intakes, 100mg in the morning or 200mg at bedtime.
In some cases, notably to help pregnancy, the doctor may increase the dose to 600 mg per day, divided into three intakes.
For threatened abortion, 200mg-400mg per day to be taken in the acute phase from the start to 12th week of pregnancy.
For menace for preterm delivery, 400 mg every 6 to 8 hours depending on the clinical response during the acute phase then a dosage of 3 x 200mg /day as maintenance treatment until the 36th week of pregnancy.
In hormone replacement therapy in post menopausal women receiving estrogen therapy, treatment can be prescribed continuously or sequentially for at least 12 days per month.

MODE OF ADMINISTRATION
Two routes of administration are possible, oral and vaginal which will be decided individually by the prescribing physician. If the medicine is to be administered orally, swallow the whole capsule with a glass of water preferably in the evening before going to bed or in to three intakes following the doctor's prescription.
If the medicine will be administered vaginally, insert each capsule deeply into the vagina. The duration of the treatment will be specified by the prescribing physician per the needs of the patient. This may be readjusted depending on the indication and efficacy of the treatment.

CONTRAINDICATIONS
Utrogestan should not be used in individuals with any of the following conditions:
- Known allergy or hypersensitivity to progesterone or to any of the excipients.
- Severe hepatic dysfunction.
- Undiagnosed vaginal bleeding.
- Known missed abortion or ectopic pregnancy
- Mammary or genital tract carcinoma.
- Thromboembolic or thrombophlebitis disorders.
- Cerebral haemorrhage.
- Porphyria.

WARNINGS AND PRECAUTIONS
Oral
Utrogestan is intended to be co-prescribed with an oestrogen product as HRT. Epidemiological evidence suggests that the use of HRT is associated with an increased risk of developing deep vein thrombosis (DVT) or pulmonary embolism. The prescribing information for the co-prescribed oestrogen product should be referred to for information about the risks of venous thromboembolism.
There is suggestive evidence of a small increased risk of breast cancer with oestrogen replacement therapy. It is not known whether concurrent progesterone influences the risk of cancer in post-menopausal women taking hormone replacement therapy. The prescribing information for the co-prescribed oestrogen product should be referred to for information about the risks of breast cancer.
Prior to taking hormone replacement therapy (and at regular intervals thereafter) each woman should be assessed. A personal and family medical history should be taken and physical examination should be guided by this and by the contraindications and warnings for this product.
Utrogestan should not be taken with food and should be taken at bedtime. Concomitant food ingestion increases the bioavailability of Utrogestan.
Utrogestan should be used cautiously in patients with conditions that might be aggravated by fluid retention (e.g. hypertension, cardiac disease, renal disease, epilepsy, migraine, asthma); in patients with a history of depression, diabetes, mild to moderate hepatic dysfunction, migraine or photosensitivity and in breast-feeding mothers.

Vaginal
During pregnancy, Utrogestan should only be used during the first three months and only by the vaginal route. Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.
Utrogestan is not suitable for use as a contraceptive.
Women should insert each capsule deep into the vagina.
-If uterine bleeding is present, do not prescribe before establishing a cause, particularly with endometrial investigations.
-Patients must be monitored closely if they have a history of venous thrombosis.
Utrogestan should be used cautiously in patients with conditions that might be aggravated by fluid retention (e.g. hypertension, cardiac disease, renal disease, epilepsy, migraine, asthma); in patients with a history of depression, diabetes, mild to moderate hepatic dysfunction, migraine or photosensitivity and in breast-feeding mothers.
Utrogestan contains soya lecithin which may cause hypersensitivity reactions (urticaria and anaphylactic shock)

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION
Progesterone is metabolized primarily by the liver. Caution should be taken with drugs that are P450 enzyme inducers and inhibitors.
Metabolism of Utrogestan is accelerated by rifamycin an antibacterial agent.
The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC50<0.1 µM), 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.
Combination with other medicinal products may decrease progesterone metabolism which may alter its effect.
This applies to:
- potent enzyme inducers such as barbiturates, antiepileptics (phenytoin), rifampicin, phenylbutazone, spironolactone and griseofulvin. These medicinal products increase hepatic metabolism.

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- some antibiotics (ampicillins, tetracyclines): changes in the intestinal flora leading to a change in the steroid enterohepatic cycle.
Utrogestan may interfere with the effects of bromocriptine and may raise the plasma concentration of cyclosporin. As these interactions, may vary between people, the clinical results are not necessarily predictable. Progestogens, but not natural progesterone may impair glucose tolerance and, because of this, increase requirements for insulin or other antidiabetic agents in diabetic patients. The bioavailability of progesterone may be reduced by smoking and increased by alcohol abuse.

PREGNANCY AND LACTATION
Effects on fertility
Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would impair fertility until the cessation of treatment.

Use in Lactation
Detectable amounts of progesterone enter the breast milk. Therefore, Utrogestan should not be used during lactation.

Paeadiatric Use
There is no experience in children as there is no relevant indication for use of Utrogestan in children

Effects on ability to drive and use machines
Cases of drowsiness and dizzy sensations have been reported for the oral form.
Drivers and machine operators are alerted to the risks of drowsiness and/or dizziness associated with oral use of this medicinal product. These problems can be avoided by taking the capsules at bedtime.

Genotoxicity
Progesterone did not induce chromosomal aberrations or sister chromatid exchanges in cultured human cells nor chromosomal aberrations or DNA strand breaks in rodent cells. Progesterone did not induce dominant lethal mutations in mice or chromosomal aberrations in the bone marrow of rats in vivo although in vivo studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg.
Weak clastogenic activity was found for progesterone in the rat hepatocyte micronucleus test after treatment with a high oral dose (100 mg/kg). Studies on transformation of rodent cells *in vitro* were inconclusive. Variable results were obtained in the mouse lymphoma tk assay. Progesterone was not mutagenic to bacteria.

Carcinogenicity
Progesterone has been shown to induce/promote the formation of ovarian, uterine, mammary, and genital tract tumors in animals. The clinical relevance of these findings is unknown. Literature data provides no indication of potential carcinogenicity in humans.
When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors and endometrial stromal sarcomas. In dogs, long-term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen.
The exposure to women remains always in the physiological range of progesterone and is regarded as hormone replacement therapy whatever the indication.

Effect on laboratory tests
Utrogestan may affect the results of laboratory tests of hepatic and/or endocrine functions.

ADVERSE EFFECTS/ UNDESIRABLE EFFECTS
Oral
Somnolence or transient dizziness may occur 1 to 3 hours after intake of the drug. Bedtime dosing and reduction of the dose may reduce these effects.
Shortening of the cycle or breakthrough bleeding may occur. If this occurs, the dose of Utrogestan can be reduced and taken at bedtime from day 1 to day 26 of each therapeutic cycle.
Acne, urticaria, rashes, fluid retention, weight changes, gastro-intestinal disturbances, changes in libido, breast discomfort, premenstrual symptoms, menstrual disturbances; also, chloasma, depression, pyrexia, insomnia, alopecia, hirsutism; rarely jaundice.
Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users.
Drowsiness and/or fleeting dizzy sensations are seen particularly with concomitant hypoestrogenism. These effects disappear immediately without compromising the benefit of treatment when doses are reduced or oestrogenization is increased.
If the treatment sequence is started too early in the month, particularly before the 15th day of the cycle, the cycle may be shortened or intercurrent bleeding may occur.
Changes in periods, amenorrhea or intercurrent bleeding have been observed and associated with the use of progesterone in general.
Vaginal
No major local intolerance issues have been reported during the different clinical trials even if some burning, pruritus or fatty discharge have been observed and reported in the literature; incidences were extremely low.
No systemic side effects, somnolence or dizziness (observed with the oral form), have been reported during clinical studies at the recommended dosages.

Overdose and treatment
Symptoms of overdose (more frequent with the oral route of administration) may include somnolence, dizziness, euphoria or dysmenorrhea. Treatment is observation and, if necessary, symptomatic and supportive measures should be provided.
Although no overdose has been reported to date for the vaginal form, the adverse effects described above are usually signs of overdose. These disappear without treatment when the dosage is reduced.

STORAGE CONDITION
Store below 30ºC. Do not refrigerate. Store in the original container
Shelf-life- 36 months

PACK SIZES
Utrogestan 100 mg – available in 1 box containing 30 capsules
Utrogestan 200 mg – available in 1 box containing 15 capsules
Two PVC/Aluminium blisters pack with an outer carton
100 mg contains 30 capsules/carton (15's+15's)
200 mg contains 15 capsules/carton (7's+8's)

Marketing Authorization Holder
Manufactured for BESINS HEALTHCARE BENELUX S.A.

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