ENDOGEST Capsules (Micronized Progesterone)

Composition

ENDOGEST 100
Each soft gelatin capsule contains
Micronized Progesterone BP .......... 100 mg
Excipients .........................................q.s.
Colour: Titanium Dioxide IP

ENDOGEST 200
Each soft gelatin capsule contains
Micronized Progesterone BP .......... 200 mg
Excipients .........................................q.s.
Colour: Titanium Dioxide IP

Dosage Form

Capsules for oral / vaginal use.

Description

ENDOGEST capsule contains micronized progesterone, which is structurally and biologically identical to progesterone of ovarian origin. Micronization increases the bioavailability of progesterone. ENDOGEST is synthesized from Mexican yam roots.

Pharmacology

Pharmacodynamics

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta and adrenal gland. Its synthesis is stimulated by LH, which primarily acts to regulate the conversion of cholesterol to pregnenolone, a progesterone precursor. It is present in highest concentrations in the ovarian corpus luteum. Progesterone is lipophilic in nature and diffuses freely into cells, where it binds to the progesterone receptors and oxen their progestational activity.

Progesterone receptors are located in the uterus, central nervous system, mammary glands and pituitary gland. The steroid receptor complex binds to DNA in the nucleus, thereby inducing the synthesis of specific proteins. Progesterone receptor concentrations are low in absence of oestrogen and increase following oestrogen administration. In the presence of adequate oestrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is essential for the development of decidual tissue and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.
Normal or near normal endometrial responses to exogenous oestrogen and progesterone have been noted in functionally
agonadal women through the sixth decade of life. Progesterone administration decreases the circulatory levels of
gonadotropins.

Pharmacokinetics

Absorption
It is well absorbed when administered orally, rectally or vaginally. When given orally, the micronized progesterone is
absorbed through the digestive tract. The rise in progesterone starts from the first hour and the highest plasma levels
are observed 1 - 3 hours after intake.
Rectal or vaginal administration or 100 - 400 mg produces concentrations in the luteal range which are maximal within 1
- 8 hours and then decline over 24 hours. Vaginal application results in avoidance of first-pass metabolism in the
gastrointestinal tract and liver, and in sustained plasma concentrations. Vaginally administered progesterone disappears
more rapidly from the circulation than the intramuscular route.

Distribution
Progesterone has a distribution phase half-life of between 3 - 6 minutes, followed by an elimination phase half-life of 19
- 95 minutes. The apparent volume of distribution is 17 - 29 L. Progesterone is taken up by fat, from which it is slowly
released. Circulating progesterone is extensively bound to plasma proteins, especially albumin and corticosteroid binding
globulin. Progesterone is approximately 96 - 99% bound to serum proteins, primarily to serum albumin (50 - 54%) and
transcortin (43 - 48%). Only small amounts are associated with erythrocytes or platelets. Concentrations in cerebrospinal
fluid are about 10% of those in the plasma.

Metabolism
Progesterone is metabolized primarily in the liver by reduction of the A-ring, hydroxylation and conjugation largely to
pregnanediols and pregnanolones. The principal metabolite is pregnanediol; other metabolites, notably 20 alpha-
dihydroprogesterone, which is present in small concentrations in plasma, and 5 alpha-pregnane-3, 20-dione, have weak
progestational activity. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulphate
metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further
metabolized in the gut via reduction, dehydroxylation and epimerization.

Excretion
Progesterone undergoes extensive biotransformation, mainly in the liver (approximately 66%) and its tissues such as
kidneys, brain, uterus and skin. The metabolites of progesterone are conjugated in the liver with glucuronic acid and
excreted primarily in the urine between 19 and 40% of a dose of labeled progesterone appears in the urine within 24
hours. A smaller quantity (8 - 17%) is excreted in the faeces and there is extensive enterohepatic circulation of
metabolites. Metabolites of progesterone are mainly excreted in the urine as glucuronide conjugates.

Indications

Infertility and Pregnancy
- Luteal support during assisted reproductive techniques (ART)
- To provide luteal support in luteal phase defects
- Threatened abortion / recurrent abortion with proven luteal phase insufficiency / defects
- Oocyte donation programme
- To prevent preterm delivery
- Treatment of puerperal depression
Menstrual Irregularities

- As progesterone challenge test in secondary amenorrhoea
- Dysfunctional uterine bleeding (DUB)

Menopause

- Premenopause
- Prevention of endometrial hyperplasia in non-hysterectomized postmenopausal women who are receiving estrogen as Hormone Replacement Therapy (HRT)

Premenstrual Syndrome

Benign Mastopathies

Dosage And Administration

A flexible dosage regimen can be followed depending on the indication and requirements of patients. A lower dose is required when vaginal route is used.

Vaginal Administration

Each capsule should be inserted deeply into the vagina. Rectal administration should be considered whenever vaginal administration is not possible.

- Luteal Support During Assisted Reproductive Techniques (IVF- ET): 200 mg thrice a day from the day of embryo transfer till pregnancy is confirmed. If pregnant, it is continued till 12th week of pregnancy.
- To Provide Luteal Support in Luteal Phase Defects: 100 mg thrice a day from the 17th day of the cycle for 10 days. If pregnant, it is continued till 12th week of pregnancy.
- Threatened Abortion / Recurrent Abortion with Proven Luteal Phase Insufficiency / Defects: 100 mg thrice a day till 12th week of pregnancy.
- Oocyte Donation Programme: 100 mg thrice daily from the day of embryo transfer till pregnancy is confirmed. If pregnant it is continued till 12th week of pregnancy.
- Prevention of Preterm Delivery: 100 mg administered once daily at bedtime from 24th - 34th week of pregnancy.
- Treatment of Puerperal Depression: 200 - 400 mg per day in divided doses for 7 days after delivery. An alternative rectal administration should be considered wherever vaginal administration in not possible.

Oral Administration

On an average in the case of deficiency or progesterone, the dosage is from 200 - 300 mg of progesterone per day once daily or in two divided doses, one in the morning one at bedtime. It is recommended to use capsule at intervals of 1 hour before or after meals. The evening dose/once daily dose is preferably taken at bedtime.

- In Secondary Amenorrhoea: 400 mg daily at bedtime for 10 days.
- DUB: 300 mg once daily from 12th day of the cycle for 10 days.
- Postmenopausal Women with Intact Uterus (in addition to oestrogen treatment): 200 mg at bedtime for the last 14 days of oestrogen per 28-day cycle. Oestrogen treatment should be administered daily at the lowest effective dose.
- Premenstrual Syndrome: 100 - 200 mg once daily from 14th day of the cycle for 10 days.
- Benign Mastopathies, Premenopause: Starting dose of 200 - 300 mg per day, 10 days per cycle, usually from 14th day until onset of menstruation.

Patients being treated with high dosage of oestrogen should be administered 300 mg daily. In such a case, patients should take 100 mg in the morning and the remaining 200 mg or 2 capsules of 100 mg at bed time. The morning dose
should be taken 2 hours after breakfast.
If a patient is being treated with 200 mg daily (total dose at bed time) and she forgets to take this dose, she should take extra dose of 1 capsule of 100 mg the following morning and continue taking rest of the capsules as prescribed. If a patient is treated with 300 mg daily and she forgets to take a morning or evening dose, she should not take the missed dose.

### Contraindications

Micronized progesterone capsules should not be used in women with any of the following conditions:
- In patients with known hypersensitivity to its ingredients.
- Vaginal route: Undiagnosed abnormal genital bleeding.
- Oral route: Serious alteration in hepatic functions.
- Known, suspected, or history of cancer of the breast.
- Active deep vein thrombosis, pulmonary embolism or history of these conditions.
- Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g. stroke, myocardial infarction).
- Liver dysfunction or disease.

### Warnings And Precautions

#### General

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Discontinue medication pending examination if there is sudden, partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema or retinal vascular lesions, medication should be withdrawn.

Natural micronized progesterone contains the hormone progesterone, which is present in significant concentrations in women during second half of menstrual cycle and during pregnancy. This should be borne in mind when treating patients with conditions that may be hormone-sensitive.

The utilization of natural micronized progesterone in the course of pregnancy is reserved to the first trimester and to the vaginal tract. Natural micronized progesterone is not a treatment against the risk of premature labour pains; the administration of micronized progesterone during the second and third trimester of pregnancy may result in appearance of severe cholestasis or hepatitis.

The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

Vaginal administration is not recommended if barrier methods of contraception are used, if patient suffers from vaginal infection (especially moniliasis) or recurrent cystitis, in patients who have recently given birth. Rectal administration is advisable in this group of patients.

Because progesterone may cause some degree of fluid retention, conditions that may be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, diabetes, mild to moderate hepatic dysfunction, photosensitivity and breastfeeding mothers require careful observation.

In cases of breakthrough bleeding, as in any cases of irregular vaginal bleeding, nonfunctional causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Patients who have a history of clinical depression should be carefully observed and the drug discontinued if the
depression recurs to a serious degree. Although concomitant use of conjugated estrogens and micronized progesterone capsules did not result in a decrease in glucose tolerance, diabetic patients should be carefully observed while receiving estrogen-progestin therapy.

It should be noted that, particularly in case of people who drive vehicles or operate machines, there is risk of drowsiness or giddiness associated with the use of this medicine. Rare instances of syncope and hypotension of possible orthostatic origin have been observed in patients taking micronized progesterone capsules.

More than half of the spontaneous premature abortions are due to genetic abnormalities. Further infectious phenomena and mechanical troubles can be responsible for abortions.

### Drug Interactions

Ketoconazole or other known inhibitors of cytochrome P4503A4 enzyme may increase the bioavailability of progesterone.

### Renal Impairment

No formal studies have evaluated the effect of renal disease on the disposition of progesterone. Since progesterone metabolites are eliminated mainly by the kidneys, micronized progesterone capsules should be used with caution and only with careful monitoring in patients with renal dysfunction.

### Hepatic Impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of progesterone. However, since progesterone is metabolized by the liver, use in patients with severe liver dysfunction or disease is contraindicated. If treatment with progesterone is indicated in patients with mild to moderate hepatic dysfunction, these patients should be monitored carefully.

### Pregnancy

The administration of this medicine in the course of the second and third trimester of pregnancy can favour the appearance of severe cholestasis or hepatitis. Reproductive studies performed in mice reveal little or no evidence of impaired fertility or harm to the fetus due to progesterone. Rare cases of congenital anomalies including cleft palate, cleft lip, ventricular septal defect, patent ductus arteriosus and other congenital heart defects have been reported in the infants of women using micronized progesterone capsules in early pregnancy.

### Lactation

Detectable amounts of progestin have been identified in the milk of nursing mothers receiving progestins. The effect of this on the nursing infant has not been determined. Hence, caution should be exercised when micronised progesterone capsules are administered to a nursing mother.

### Paediatric Use

Natural micronized progesterone should not be used in children.

### Geriatric Use

Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.
Undesirable Effects

Micronized progesterone is devoid of oestrogenic, androgenic and mineralocorticoid effects.

**Oral Route**

Drowsiness or giddiness may arise 1 - 3 hours after ingestion of the product. At times, there can be breast tenderness and abdominal bloating. In case of drowsiness after 1 - 3 hours of oral administration, the dosage may be reduced or the patient may be put on once daily evening dose. Alternatively, the vaginal route of administration of the drug could be used.

**Vaginal / Rectal Route**

Soreness, diarrhoea, flatulence, irritation or dryness may occur when administered by these routes. As with other vaginal and rectal preparations, some leakage of the capsule base may occur.

**Menses**

The menstrual cycle may be shortened or there may be intermenstrual bleeding. Menstruation may occur earlier than expected, or more rarely menstruation may be delayed. In case of shortening of menstrual cycle or intermittent bleeding shift the initiation of treatment to a later date (e.g. 19th day of cycle instead of 17th day).

**Overdosage**

No studies on overdosage have been conducted in humans. In the case of overdosage, micronized progesterone capsules should be discontinued and the patient should be treated symptomatically. Symptoms of overdosage may include somnolence, dizziness, euphoria or dysmenorrhoea. Treatment is observation and, if necessary, symptomatic and supportive measures should be provided.

Storage And Handling Instructions

Store in a cool dry place. Protect from light.

Packaging Information

ENDOGEST 100 is available in a blister pack of 10 capsules.
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