FOR USE OF REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL ONLY

Micronised Progesterone Soft Gelatin Capsules

www.greencrossindia.com

PLACENTA

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA FOR OESTROGEN PLUS PROGESTIN THERAPY

Oestrogens plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. The Women's Health Initiative (WHI) oestrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism, and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated oestrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. The Women’s Health Initiative Memory Study (WHIMS) oestrogen plus progestin ancillary study of the WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older.

COMPOSITION

PLACENTA 100
Each soft gelatin capsule contains
Micronized Progesterone ........ 100 mg

PLACENTA 200
Each soft gelatin capsule contains
Micronized Progesterone ........ 200 mg

Capsules for oral / vaginal use

PHARMACOLOGY

Pharmacodynamics

PLACENTA capsules are a dosage form of micronized progesterone which is chemically identical to progesterone of ovarian origin. The oral bioavailability of progesterone is increased through micronization.

Pharmacokinetics

(1) Oral

➤ Absorption

After oral administration of progesterone as a micronised soft-gelatin capsule formulation, maximum serum concentrations are attained within 3 hours. The absolute bioavailability of micronised progesterone is not known. The table summarizes the mean pharmacokinetic parameters in postmenopausal women after five oral daily doses of micronized progesterone capsules

Serum progesterone concentrations appeared linear and dose proportional following multiple dose administration of micronized progesterone capsules 100 mg over the dose range 100 mg/day to 300 mg/day in postmenopausal women. Although doses greater than 300 mg/day were not studied in females, serum concentrations from a study in male volunteers appeared linear and dose proportional between 100 mg/day and 400 mg/day. The pharmacokinetic parameters in male volunteers were generally consistent with those seen in postmenopausal women.

➤ Distribution

Progesterone is approximately 96% to 99% bound to serum proteins, primarily to serum albumin (50% to 54%) and transcortin (43% to 48%).

➤ Metabolism

Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. 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**

The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. Progesterone metabolites are eliminated mainly by the kidneys. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the faeces.

**2) Vaginal**

Vaginal application results in avoidance of first-pass metabolism in the gastrointestinal tract and liver, and in sustained plasma concentrations. After vaginal administration of progesterone, plasma progesterone levels reach maximal concentrations within 3-8 hours, depending on the formulation used and gradually fall during the next 8 hours. Vaginally administered progesterone disappears more rapidly from the circulation than the I.M. Furthermore, higher doses are necessary of vaginal progesterone (100 mg) than of I.M. progesterone (25 mg) in order to achieve serum progesterone concentrations of the luteal phase range. The comparison of the same doses (300 mg) of micronized progesterone in a non-liquefying cream vaginally and capsules of micronized progesterone orally favoured the use of the vaginal formulation, since all the patients achieved luteal phase progesterone concentrations in the vaginal group compared with only two out of five patients in the oral group.

**INDICATIONS**

**1) 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

**2) Menstrual Irregularities**
- As progesterone challenge test in secondary amenorrhoea
- Dysfunctional uterine bleeding (DUB)

**3) Postmenopausal women**
- Prevention of endometrial hyperplasia in non-hysterectomised postmenopausal women who are receiving estrogen as Hormone Replacement Therapy (HRT)

**4) Premenstrual syndrome**

**DOSAGE AND ADMINISTRATION**

Flexible dosage regimen can be followed depending on the indication and requirements of patients. 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):**
  **PLACENTA** 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:**
  **PLACENTA** 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:**
  **PLACENTA** 100 mg thrice a day till 12th week of pregnancy.
- **Oocyte donation programme:**
  **PLACENTA** 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:**
  **PLACENTA** 100 mg administered once daily at bedtime from 24th to 34th week of pregnancy.

  **Oral Administration**
  The evening dose/once daily dose is preferably taken at bedtime.

- **In secondary amenorrhoea:**
  **PLACENTA** 200 mg twice daily for 10 days.

- **Postmenopausal women with intact uterus (in addition to estrogen treatment):**
  **PLACENTA** 200 mg at bed time for 12 days sequentially per 28 day cycle.

- **Premenstrual syndrome:**
  **PLACENTA** 100-200 mg once daily from 14th day of the cycle for 10 days.

**CONTRAINDICATIONS**

**PLACENTA** capsules should not be used in women with any of the following conditions:

1. In patients with known hypersensitivity to its ingredients.
2. Undiagnosed abnormal genital bleeding.
3. Known, suspected, or history of cancer of the breast.
4. Active deep vein thrombosis, pulmonary embolism or history of these conditions.
5. Active arterial thromboembolic disease (for example, stroke and myocardial infarction), or a history of these conditions.
6. Known liver dysfunction or disease.
7. Known or suspected pregnancy.

**WARNINGS AND PRECAUTIONS**

**General**

**Cardiovascular disorders**

An increased risk of pulmonary embolism, deep vein thrombosis (DVT), stroke, and myocardial infarction has been reported with oestrogen plus progestin therapy. Should any of these occur or be suspected, oestrogen with progestin should be discontinued immediately. Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history or family history of venous thromboembolism [VTE], obesity, and systemic lupus erythematosus) should be managed appropriately.

**Stroke**

In the Women’s Health Initiative (WHI) oestrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in all women receiving daily conjugated oestrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) compared to placebo (33 versus 25/10,000 women-years). The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, oestrogen plus progestin therapy should be discontinued immediately.

**Coronary Heart Disease**

In the WHI oestrogen plus progestin substudy, there was a statistically nonsignificant increased risk of CHD events (defined as nonfatal MI, silent MI, or CHD death) reported in women receiving daily CE/MPA compared to women receiving placebo (41 versus 34/10,000 women-years). An increase in relative risk was demonstrated in year 1 and a trend toward decreasing relative risk was reported in years 2 through 5. In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Oestrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. 2,321 women from the original HERS trial agreed to participate in an open-label extension of HERS.
HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall. Venous Thromboembolism (VTE) In the WHI oestrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and pulmonary embolism [PE]), was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17/10,000 women-years) and PE. Statistically significant increases in risk for both DVT (26 versus 13/10,000 women-years) and PE (18 versus 8/10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted. Should a VTE occur or be suspected, oestrogen plus progestin therapy should be discontinued immediately. If feasible, oestrogens with progestins should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant neoplasms

Breast Cancer

The most important randomized clinical trial providing information about breast cancer is the Women’s Health Initiative (WHI) substudy of daily CE (0.625 mg) plus MPA (2.5 mg). In the oestrogen plus progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer in women who took daily CE plus MPA. In this substudy, prior use of oestrogen alone or oestrogen plus progestin therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24 (95% nCI 1.01 - 1.54), and the absolute risk was 41 versus 33 cases/10,000 women-years for oestrogen plus progestin compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases/10,000 women-years, for oestrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases/10,000 women-years for oestrogen plus progestin compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups. The use of oestrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed oestrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed oestrogen users is about 2 to 12 times greater than in nonusers, and appears dependent on duration of treatment and on oestrogen dose. Most studies show no significant increased risk associated with the use of oestrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after oestrogen therapy is discontinued. Clinical surveillance of all women using oestrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural oestrogens results in a different endometrial risk profile than synthetic oestrogens of equivalent oestrogen dose. Adding a progestin to oestrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor of endometrial cancer.

Ovarian Cancer

The WHI oestrogen plus progestin substudy reported a statistically nonsignificant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95% nCI, 0.77 - 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases/10,000 women-years. In some epidemiologic studies, the use of oestrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies and some report no association.

Probable dementia

In the oestrogen plus progestin Women’s Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. In the WHIMS oestrogen plus progestin ancillary study, after an
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average followup of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for oestrogen plus progestin versus placebo was 2.05 (95% CI 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases/10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women.

Vision abnormalities
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 papilledema or retinal vascular lesions, medication should be permanently discontinued.

Addition of a progestin when a woman has not had a hysterectomy
Studies of the addition of a progestin for 10 or more days of a cycle of oestrogen administration, or daily with oestrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with oestrogens compared with oestrogen-alone regimens. These include a possible increased risk of breast cancer.

Fluid retention
Progesterone may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation.

Dizziness and drowsiness
Micronized progesterone capsules may cause transient dizziness and drowsiness and should be used with caution when driving a motor vehicle or operating machinery. PLACENTA capsules should be taken as a single daily dose at bedtime.

Drug interactions
Ketoconazole or other known inhibitors of cytochrome P450 3A4 enzyme may increase the bioavailability of progesterone.

Drug-laboratory test interactions
The following laboratory results may be altered by the use of oestrogen-progestin combination drugs:
- Increased sulfobromophthalein retention and other hepatic function tests.
- Coagulation tests: increase in prothrombin factors VII, VIII, IX and X.
- Pregnanediol determination.
- Thyroid function, increase in PBI, and butanol extractable protein bound iodine and decrease in T3 uptake values.

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, micronised 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 metabolised 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
Pregnancy Category B.
PLACENTA capsules should not be used during pregnancy.

Lactation
Detectable amounts of progestin have been identified in the milk of nursing mothers receiving progestins. Caution should be exercised when PLACENTA capsules are administered to a nursing woman.

Paediatric use
PLACENTA capsules are not indicated for paediatric use and no clinical data have been collected in children.

**Geriatric Use**
Clinical studies of micronized progesterone capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. The Women's Health Initiative Study In the Women's Health Initiative (WHI) oestrogen plus progestin substudy, there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age. The Women's Health Initiative Memory Study In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in the oestrogen plus progestin ancillary study when compared to placebo.

**UNDESIRABLE EFFECTS**
Micronised progesterone is devoid of oestrogenic, androgenic and minerelocorticoid effects. Common adverse effects are drowsiness, dizziness, breast tenderness and abdominal bloating. Side effects are less when vaginal route is used. Vaginal Irritation is the most common side effect with vaginal use.

**Postmarketing experience**
The following additional adverse reactions have been reported with micronized progesterone capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

**Genitourinary System:** endometrial carcinoma, hypospadia, intra-uterine death, menorrhagia, menstrual disorder, metrorrhagia, ovarian cyst, spontaneous abortion.

**Cardiovascular:** circulatory collapse, congenital heart disease (including ventricular septal defect and patent ductus arteriosus), hypertension, hypotension, tachycardia.

**Gastrointestinal:** acute pancreatitis, cholestasis, cholestatic hepatitis, dysphagia, hepatic failure, hepatic necrosis, hepatitis, increased liver function tests (including alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased), jaundice, swollen tongue.

**Skin:** alopecia, pruritus, urticaria.

**Eyes:** blurred vision, diplopia, visual disturbance.

**Central Nervous System:** aggression, convulsion, depersonalization, depressed consciousness, disorientation, dysarthria, loss of consciousness, paresthesia, sedation, stupor, syncope (with and without hypotension), transient ischemic attack, suicidal ideation. During initial therapy, a few women have experienced a constellation of many or all of the following symptoms: extreme dizziness and/or drowsiness, blurred vision, slurred speech, difficulty walking, loss of consciousness, vertigo, confidence, disorientation, feeling drunk, and shortness of breath.

**Miscellaneous:** abnormal gait, anaphylactic reaction, arthralgia, blood glucose increased, choking, cleft lip, cleft palate, difficulty walking, dyspnoea, face oedema, feeling abnormal, feeling drunk, hypersensitivity, asthma, muscle cramp, throat tightness, tinnitus, vertigo, weight decreased, weight increased.

**OVERDOSAGE**
No studies on overdosage have been conducted in humans. In the case of overdosage, micronised progesterone capsules should be discontinued and the patient should be treated symptomatically.

**STORAGE AND HANDLING INSTRUCTIONS**
Store in a cool dry place. Protect from light.

**PACKAGING INFORMATION**
PLACENTA 100 is available in a blister pack of 10 capsules.
PLACENTA 200 is available in a blister pack of 10 capsules.