UNILAB

Progesterone

Heragest®

200 mg Soft Gelatin Capsules
Progestogens
ATC Code - G03DA

℞

FORMULATION
Each soft gelatin capsule contains:
Progesterone BP (Natural, Micronized).....200 mg

PHARMACOLOGIC CATEGORY
Progestogens (ATC Code – G03DA)

PRODUCT DESCRIPTION
Progesterone (Heragest) 200 mg Soft Gelatin Capsule is a cream, oval, soft gelatin capsule containing a pale yellow oily paste.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Progesterone is a hormone produced in the ovaries (specifically the corpus luteum), the adrenal glands and in the placenta during pregnancy. It acts on the endometrium by converting the proliferating phase to the secretory phase. Progesterone is capable of inducing a normal full secretory endometrium and in particular, gestagenic, antiestrogenic, slightly antiandrogenic, and antialdosterone effects.

Pharmacokinetics
Micronized progesterone is absorbed in the gastrointestinal tract. After oral administration of 2 capsules (each capsule contains 200 mg progesterone) of progesterone in healthy volunteers, an increase in plasma progesterone levels to a maximum concentration of 13.8 ng/mL ± 2.9 ng/mL in 2.2 ± 1.4 hours was observed. 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.

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

Progesterone is metabolized primarily by the liver. The main plasma metabolites are 20α hydroxy-Δ 4α-prenolone and 5α-dihydrogesterone. Some progesterone metabolites are excreted in the bile and these may be conjugated and further metabolized in the gut via reduction, dehydroxylation and epimerization. The main plasma and urinary metabolites are similar to those found during the physiological secretion of the corpus luteum.

Progesterone is eliminated in the urine (95%) in the form of glycuroconjugated metabolites, mainly 3α, 5β-pregnanediol (pregnandiol).

Vaginal
First-pass metabolism in the gastrointestinal tract and liver is bypassed when progesterone is administered vaginally. After administration, plasma progesterone levels reach maximal concentrations within 3 to 8 hours, depending on the formulation used and gradually fall during the next 8 hours.

INDICATIONS
Infertility and Pregnancy
- Provide luteal support in luteal phase defects in threatened/recurrent abortion
- Prevent preterm delivery

Luteal phase insufficiency
- Progesterone challenge test in secondary amenorrhea
- Dysfunctional uterine bleeding (DUB)
- Menstrual irregularities due to dysovulation or anovulation
- Premenstrual syndrome
- Fibrocystic mastopathy
- Dysmenorrhea
- Premenopause

Postmenopausal women
- Prevention of endometrial hyperplasia in postmenopausal women with intact uterus who are receiving estrogen as hormone replacement therapy

DOSAGE AND MODE OF ADMINISTRATION
For oral or vaginal administration, as directed by a physician.

ORAL ADMINISTRATION
Progesterone should be taken at bedtime. Do ***not*** administer with food. In women who experience difficulty swallowing the capsules, take the capsules with a glass of water while in standing position.

Indication	Natural Micronized Progesterone Oral Dose
Threatened abortion/recurrent abortion with luteal phase defect	200 to 600 mg daily
Preterm delivery	400 mg every 6 to 8 hours depending on acute phase, then supporting dose of 600 mg/day divided into 3 doses until 36th week of pregnancy
Progesterone challenge test in secondary amenorrhea	400 mg daily at bedtime for 10 days
Dysfunctional uterine bleeding, Menstrual irregularities due to dysovulation or anovulation	200 mg once daily from 17th day of the cycle for 10 days
Premenstrual syndrome, Fibrocystic mastopathy, Dysmenorrhea, Premenopause	200 or 400 mg per day taken for 10 days (usually beginning from the 14th to 17th day to complete 10 days)
Prevention of endometrial hyperplasia in postmenopausal women with intact uterus who are receiving estrogen as hormone replacement therapy	200 mg at bedtime for 12 days sequentially per 28 day cycle
Or, as directed by a physician	

VAGINAL ADMINISTRATION
Each progesterone capsule should be inserted deeply into the vagina. Rectal administration should be considered whenever vaginal administration is not possible. Concomitant use with other intravaginal preparations is ***not*** recommended since the possibility exists that there may be changes in the release and absorption of progesterone from the vaginal insert.

Indication	Natural Micronized Progesterone Vaginal Dose
Luteal support in assisted reproductive techniques [e.g., *in vitro* fertilization-embryo transfer (IVF-ET)]	200 mg three times daily from embryo transfer until pregnancy is confirmed. If pregnant, progesterone is continued up to 12th week of pregnancy.
Or, as directed by a physician	

CONTRAINDICATIONS
- Hypersensitivity to progesterone, or to any ingredient in the product
- In patients allergic to peanuts; the product contains peanut (arachis) oil
- Active liver disease, especially of the obstructive type
- History of known or suspected estrogen-dependent or progestin-dependent malignant neoplasia (e.g., breast cancer or endometrial cancer)
- Undiagnosed abnormal genital bleeding
- Active or past history of arterial thromboembolic disease (e.g., stroke, myocardial infarction, coronary heart disease)
- Classical migraine
- Cerebral hemorrhage
- Active or past history of confirmed venous thromboembolism (*i.e.*, deep venous thrombosis or pulmonary embolism) or active thrombophlebitis
- Partial or complete loss of vision due to ophthalmic vascular disease
- Missed or incomplete abortion
- Not intended for pregnancy test
- Porphyria

WARNINGS AND PRECAUTIONS
General
Progestins are usually coadministered with estrogens. Some of the information in this section pertaining to combined estrogen-progestin therapy may therefore not apply to progestin-only therapy. Physician discretion is advised.

Estrogen Plus Progestin in Menopausal Hormone Therapy
Endometrial Hyperplasia
Estrogen, as a single systemic agent, is appropriate in women after hysterectomy. Otherwise, addition of micronized progesterone/progestogen is required for endometrial protection.

Estrogens plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia.

Progestogens are not alike with regard to potential adverse metabolic effects, cognitive effects or associated breast cancer risk when combined with systemic estrogen therapy.

Micronized progesterone used with estradiol may be associated with a better safety profile than synthetic progestins with regard to breast cancer and cardiovascular risk.

Physical Examinations
- Patients should be assessed prior to (and at regular intervals thereafter) taking hormone replacement therapy (HRT). Physical examination (including special attention to the breast and pelvic organs) and a Pap smear should be done. This should be guided by personal and family medical history and by the contraindications and warnings of this product.
- Endometrial biopsy should be done when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides, cholesterol, and liver function tests.
- The first follow-up examination should be done within 3 to 6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals of at least once a year. Appropriate investigations should be arranged at regular intervals determined by the physician.
- Patients are encouraged to practice frequent self-examination of the breasts.

Stroke
The risk of ischemic stroke has been shown to be increased during the first year of treatment with continuous-combined conjugated estrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg) in postmenopausal women (50 to 79 years old) compared to those receiving placebo. Estrogen plus progestin therapy should be discontinued immediately should a stroke occur or be expected.

Coronary Artery Disease (CAD)
Randomized controlled trials have shown no evidence of cardiovascular benefit with the use of continuous-combined conjugated estrogens and medroxyprogesterone acetate. This was demonstrated in the Women's Health Initiative (WHI) and Heart and estrogen/progestin Replacement Study (HERS) which showed a possible increased risk of cardiovascular morbidity in the first year of use with no overall benefit.

High Blood Pressure
Monitor blood pressure in women using HRT. Elevation of blood pressure has been observed in patients using HRT. This elevation in blood pressure should be investigated in previously normotensive or hypertensive patients. In such cases, HRT may have to be discontinued.

Venous Thromboembolism (VTE)
A higher relative risk of developing VTE (i.e., deep vein thrombosis or pulmonary embolism) is observed with the use of estrogen or estrogen-progesterone HRT.

Personal history or family history, severe obesity (body mass index, BMI >30 kg/m^2), age and smoking are the generally recognized factors for VTE.

Prolonged immobilization, major trauma or major surgery may temporarily increase the risk of VTE. As with all postoperative patients, attention should be given to prophylactic measures to prevent VTE after surgery. HRT should be temporarily stopped 4 to 6 weeks earlier (if possible) in instances where prolonged immobilization is likely to follow elective surgery, particularly abdominal surgery or orthopedic surgery to the lower limbs. Do not restart therapy until the patient is completely mobilized. Also, close supervision is advised in patients with varicose veins.

Progesterone should be discontinued in case VTE is suspected or develops after initiation of therapy.

Fluid Retention
Use progesterone with caution 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 breastfeeding mothers.

Glucose and Lipid Metabolism
A significant percentage of peri- and postmenopausal patients taking progestins has been shown to develop worsening of blood glucose tolerance and lipid metabolism. Closely observe diabetic patients or those with a predisposition to diabetes to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

Calcium and Phosphorus Metabolism
The prolonged use of estrogens, with or without progestins, influences calcium and phosphorus metabolism. Patients with metabolic and malignant bone diseases associated with hypercalcemia and patients with renal insufficiency should use estrogens (with or without progestins) with caution.

Familial Hyperlipidemias or Porphyria
Women with familial hyperlipidemias or porphyria need special surveillance. Additional lipid-lowering measures are recommended as appropriate.

Breast Cancer
It is suggested that estrogen plus progestin therapy may cause a mild increase in the risk of breast cancer. Although it is not known whether this also occurs with concurrent progesterone therapy, patients should refer to the prescribing information for the co-prescribed estrogen for information about the risk of breast cancer.

Estrogens with or without progestins is not recommended to be given to women with existing breast cancer or those with a history of the disease. Caution is advised in prescribing estrogens with or without progestins in women with known risk factors associated with the development of breast cancer such as strong family history of breast cancer (first degree relative) or one previous breast condition with an increased risk (abnormal mammograms and/or atypical hyperplasia at breast biopsy). Nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated for these are known factors for the development of breast cancer.

An increase in abnormal mammograms has been observed with the use of progestin plus estrogen therapy. Further evaluation is required to confirm these results. All women should receive yearly breast examinations (by a healthcare provider) and perform monthly breast self-examinations. Mammography examinations should be scheduled based on patient age, risk factors and prior mammogram results.

The degree of association between breast cancer and menopause hormone therapy (MHT) remains controversial. Most long-term studies reflect the use of one specific combination of oral estrogen and progestogen and suggest a possible increased risk with increasing duration. Three studies suggest that micronized progesterone could be associated with a lower risk than synthetic progestogen. A large European observational study suggested that micronized progesterone used in association with oral or percutaneous estradiol may be associated with a better risk profile for breast cancer than synthetic progestogens. A case-control study from France also showed a lower level of risk with progesterone than synthetic progestogens.

The increased risk of breast cancer is primarily associated with the addition of a synthetic progestogen to estrogen therapy (conjugated estrogen and medroxyprogesterone acetate continuous combined therapy) and related to the duration of use. The risk may be lower with micronized progesterone than with a synthetic progestogen. The risk of breast cancer attributable to MHT is small and the risk decreases progressively after treatment is stopped.

Endometrial Cancer
When estrogens are administered alone or for prolonged periods, the risk of endometrial hyperplasia and carcinoma is increased.

Progestins may cause breakthrough bleeding and spotting bleeding during the first months of treatment. If these symptoms are still present after 6 months of treatment, if it starts beyond that time or if it continues after treatment has been discontinued, advise patients to report to their doctor and be referred for gynecological investigation. In such cases, diagnostic measures (e.g., endometrial biopsy or curettage) must be undertaken to rule out the possibility of uterine malignancy and treatment should be re-evaluated in these patients. The addition of progesterone to estrogen-only HRT for 10 or more days per cycle greatly reduces this risk in non-hysterectomized women.

Ovarian Cancer
Some epidemiological studies have shown that long-term use (at least 5 years or more) of estrogen plus progestin and estrogen-only HRT products has been associated with an increased risk of ovarian cancer. However, it is uncertain whether long-term use of combined HRT confers a different risk than estrogen-only products.

Cerebrovascular Insufficiency
Discontinue therapy if patient experiences visual disturbances, classical migraine, transient aphasia, paralysis, or loss of consciousness during therapy.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be re-evaluated.

Dementia
Although some evidence exist from the WHI trial of increased risk of probable dementia in women who start using continuous combined conjugated estrogen and medroxyprogesterone acetate after 65 years old, it is not known whether these findings apply to younger postmenopausal women or other HRT products.

Pre-existing Mental Depression
Use progesterone with caution in patients with pre-existing mental depression. Progesterone should be discontinued if depression recurs to a serious degree during therapy.

Visual Effects
Retinal vascular thrombosis has occurred in patients receiving estrogen. Estrogen plus progesterone therapy should be withheld if unexplained, sudden or gradual, partial or complete loss of vision, proptosis or diplopia, papilledema, retinal vascular lesions, or migraine occurs. Appropriate and therapeutic measures should be instituted in these patients. Discontinue permanently if examination reveals papilledema or retinal vascular lesions.

Carcinogenicity, Mutagenesis, Impairment of Fertility
Progesterone, when implanted into female mice, produced mammary carcinomas, ovarian granulosa cell tumors and endometrial stromal carcinomas. Long-term intramuscular (IM) injections in dogs produced nodular hyperplasia and benign and malignant mammary tumors. Rats that were given subcutaneous (SC) or IM injections of progesterone and were previously treated with chemical carcinogen had a lower latency period and an increased incidence of mammary tumors. Progesterone has not been tested for carcinogenicity in animals by the oral route of administration.

In *in vitro* studies, progesterone did not show evidence of genotoxicity for point mutations or for chromosomal damage. In *in vivo* studies, however, chromosomal damage was present in mice at oral doses of 1000 mg/kg and 2000 mg/kg. Inhibition of ovulation has been shown in a number of species when progesterone is administered exogenously. Impaired fertility is expected when progesterone is given at high doses and for an extended duration until treatment is stopped.

Effects on the Ability to Drive and Use Machines
Progesterone use may result in transient and occasional somnolence or dizziness/drowsiness which usually occurs 1 to 4 hours after ingestion. This condition may be aggravated when progesterone is administered with food. Patients should be warned that visual symptoms may make activities such as driving or operating machinery more hazardous than usual under conditions of variable lighting. Taking the capsules at bedtime should reduce these effects during the day.

INTERACTIONS WITH OTHER MEDICAMENTS
Drugs Inducing Liver Enzymes (e.g., carbamazepine, griseofulvin, barbiturates, hydantoins, meprobamates, phenylbutazone, or rifampicin): The metabolism of progesterone may be enhanced and its activity reduced by compounds that induce liver enzymes.
Cytochrome P450 Inhibitors: Ketoconazole (an inhibitor of CYP450 3A4) inhibited the metabolism of progesterone. An increase in the bioavailability of progesterone may be expected; however, the relevance of this *in vitro* finding is unknown.
The bioavailability of medroxyprogesterone acetate may be significantly reduced when concomitantly administered with aminoglutethimide. It is unknown whether this interaction occurs with progesterone.
Antidiabetic Agents: Progesterone can decrease glucose tolerance and therefore an adjustment in the antidiabetic dosage may be required.
Bromocriptine: Bromocriptine inhibits prolactin. This may interfere with the effects of progesterone resulting in a decreased progesterone action.
Ciclosporin: Progesterone may inhibit ciclosporin metabolism leading to increased plasma ciclosporin concentrations.
Conjugated Estrogens: Coadministration of conjugated estrogens and progesterone resulted in an increase in total estrone concentrations and total equilin concentrations and a decrease in circulating 17β estradiol concentration. The half-life of the conjugated estrogens was similar with coadministration of progesterone.
Herbal Products: Some herbal products such as St John's Wort may reduce the effect of progesterone.
Food: Food increases the bioavailability of progesterone relative to a fasting state when administered at a dose of 200 mg. Progesterone significantly increases AUC and C_{max} values with no effect on T_{max}.
The following laboratory results may be altered by the use of estrogen and progestin therapy: Increased sulfobromophthalein retention and other hepatic function tests, coagulation tests (increase in prothrombin factors VII, VIII, IX, and X), pregnanediol determination, thyroid function (increases in PBI, and butanol extractable protein bound iodine and decrease in T3 uptake values)

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: Pregnancy Category B. Progesterone may delay spontaneous abortion of fertilized defective ova because of their uterine-relaxant effects. Also, the common cause of abortion in most women is defective ovum which progesterone could not be expected to influence.

There is evidence of potential adverse effects on the fetus when the drug is administered during the first 4 months of pregnancy. Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis. A case of cleft palate was reported. When used for unapproved uses, rare cases of fetal death (causality not established) have been reported.

Lactation: Progesterone is excreted in human milk. Since the possible effects of progesterone on the breastfeeding infant have not been determined, caution should be exercised when progesterone is administered to breastfeeding mothers.

Pediatric: Progesterone is not intended for use in children. No clinical studies in pediatric population have been conducted.

Geriatric: In the WHI estrogen plus progestin substudy, there was a higher relative risk of nonfatal stroke and invasive breast cancer in women >65 years old. There was an increased risk of developing probable dementia in WHIMS estrogen plus progestin ancillary study in women aged 65 to 79 years. However, no sufficient numbers of geriatric women are involved in clinical studies to determine if there is a difference in the response of women over 65 years from the younger subjects to progesterone.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of progesterone has not been studied. However, since sexual hormones are metabolized in the liver, progesterone should be used with caution in these patients.

Liver function tests should be done regularly in patients who are suspected of having hepatic disease.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of progesterone has not been studied.

UNDESIRABLE EFFECTS
Infections and infestations: Upper respiratory infection, viral infection
Neoplasms, benign, malignant and unspecified (incl cysts and polyps): Breast carcinoma
Blood and lymphatic system disorders: Jaundice
Immune system disorders: Anaphylaxis/anaphylactic reaction, angioedema, asthma, erythema multiforme, erythema nodosum, facial edema, hypersensitivity, urticaria
Endocrine disorders: Hirsutism, masculinization of female fetus, ovarian hyperstimulation syndrome
Metabolism and nutrition disorders: Changes in appetite, changes in body weight, edema, fluid retention, sodium retention
Psychiatric disorders: Aggression, anxiety/worry, confusion, depersonalization, disorientation, drowsiness, dysarthria/slurred speech, emotional lability, impaired concentration, insomnia, mental depression, mood change, nervousness, somnolence, stupor, suicidal ideation, throat tightness
Nervous system disorders: Aggravation of migraine episodes, convulsion, depressed level of consciousness, difficulty walking/gait disturbance, dizziness, headache, loss of consciousness, neuritis, paresthesia, sedation, vertigo
Eye disorders: Blurred vision, contact lens intolerance, diplopia, neuro-ocular lesions (e.g., retinal thrombosis, optic neuritis), steepening of the corneal curvature, visual disturbances
Ear and labyrinth disorders: Tinnitus
Cardiac disorders: Chest pain, coronary thrombosis, dyspnea, palpitation, tachycardia
Vascular disorders: Circulatory collapse, hot flush, hypertension, hypotension, syncope (with and without hypotension), thromboembolic disorders, thrombophlebitis, transient ischemic attack (TIA), venous thromboembolism (i.e., deep leg or pelvic venous thrombosis or pulmonary embolism)
Respiratory, thoracic and mediastinal disorders: Choking, cough, nasopharyngitis
Gastrointestinal disorders: Abdominal discomfort (cramps, pressure, bloating, pain), acute pancreatitis, constipation, diarrhea, dysphagia, gastrointestinal disturbance, nausea, swollen tongue, vomiting
Hepatobiliary disorders: Asymptomatic impaired liver function, cholestasis, cholestatic hepatitis, cholestatic jaundice, gallbladder disorder, hepatic failure, hepatic necrosis, hepatitis, hepatocellular liver disease (rare)
Skin and subcutaneous tissue disorders: Acne, chloasma (melasma), eczema, hair loss (alopecia), hemorrhagic eruption, pruritus, rash
Musculoskeletal and connective tissue disorder: Arthralgia, back pain, muscle cramp, musculoskeletal pain
Renal and urinary disorders: Cystitis, dysuria, urinary problems, urinary tract infection
Pregnancy, puerperium and perinatal conditions: Spontaneous abortion
Reproductive system and breast disorders: Altered menstrual cycle or irregular menstrual bleeding, breast discomfort, breast pain, breast tenderness, change in libido, changes in cervical erosion and amount of cervical secretion, dysmenorrhea, dyspareunia, endometrial carcinoma, endometrial hyperplasia, gynecomastia, heavier menses (menorrhagia), hypospadias, menstrual disorder, metrorrhagia, ovarian cyst, perineal pain, premenstrual like syndrome, reactivation of endometriosis, shortening of the menstrual cycle or breakthrough bleeding, spotting, uterine hemorrhage, vaginal discharge, vaginal dryness, vaginal itching, vaginal mycosis
Congenital, familial and genetic disorders: Cleft lip, cleft palate, congenital heart disease (including ventricular septal defect and patent ductus arteriosus)
General disorders and administration site conditions: Fatigue, feeling abnormal, feeling drunk, fetal death, fever, irritability, lethargy, malaise, night sweats, pain, peripheral swelling
Investigations: Altered coagulation tests, altered lipid profile, breast excisional biopsy, decreased glucose tolerance, decreased weight, increased blood glucose level, increased blood pressure, increased liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase), increased weight
Surgical and medical procedures: Need for cholecystectomy

OVERDOSE AND TREATMENT
The toxicity of progesterone is very low. Symptoms that may occur include nausea, vomiting, somnolence, dizziness, euphoria, or dysmenorrhea. Appropriate supportive measures should be performed and progesterone should be discontinued in cases of overdose.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Protect from heat, light, and excess humidity.
Keep the product out of reach and sight of children
Store in original packaging.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph.
By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Clear PVC Blister Pack x 10's (Box of 100's)

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Reg. IPOPHIL
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CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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Manufactured by:
Sterii-Gene Life Sciences (P) Ltd.
No. 45 Mangalam Main Road, Mangalam Village
Villianur Commune, Puducherry – 605110, India

Imported and Distributed by:
UNILAB, Inc.
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

Trusted Quality Healthcare

UNILAB Consumer Care
8-UNILAB-1
8-864522-1
Provincial Toll Free: 1-800-10-8645221
Email: info@unilab.com.ph
Website: www.unilab.com.ph

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