PRODUCT MONOGRAPH

[Pr]PROGESTERONE

Progesterone Capsules
100 mg

Progestin

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Pr **PROGESTERONE**
Progesterone Capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	All Non-medicinal Ingredients
Oral	Capsule 100 mg	Ammonium Hydroxide, Butyl Alcohol, Black Iron Oxide, Gelatin, Glycerin, Isopropyl Alcohol, Lecithin, Light Mineral Oil, Purified Water, Propylene Glycol, Shellac Glaze, Sunflower Oil and Titanium Dioxide

INDICATIONS AND CLINICAL USE

PROGESTERONE (micronized progesterone) is indicated for:

- Women with an intact uterus as an adjunct to postmenopausal estrogen replacement therapy to significantly reduce the risk of endometrial hyperplasia and carcinoma.

CONTRAINDICATIONS

PROGESTERONE is contraindicated in patients with any of the following disorders:

- hypersensitivity to this drug, soya, peanut or to any ingredient in the formulation of the capsule. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph;
- liver dysfunction or disease as long as liver function tests have failed to return to normal;
- personal history of known or suspected estrogen-dependent or progestin-dependent malignant neoplasia (e.g. breast cancer or endometrial cancer)
- endometrial hyperplasia;
- undiagnosed abnormal genital bleeding;
- known or suspected pregnancy;
- active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease)
- classical migraine;
- active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis;
- partial or complete loss of vision due to ophthalmic vascular disease.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of combined *estrogen plus progestin* therapy (n=16,608) and *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.[31, 30, 2]

The *estrogen plus progestin* arm of the WHI trial indicated an increased risk of *myocardial infarction* (MI), *stroke, invasive breast cancer, pulmonary embolism and deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.[31]

The *estrogen-alone* arm of the WHI trial indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.[30]

The Women's Health Initiative Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older.

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins should not be prescribed for primary or secondary prevention of cardiovascular diseases or dementia.
- Estrogens with or without progestins should be prescribed at the lowest effective dose for the approved indication.
- Estrogens with or without progestins should be prescribed for the shortest period possible for the approved indication.

Some of the information presented in the Warnings and Precautions section is provided in light of the fact that progestin medication is often prescribed concomitantly with an estrogen medication. Information in this section pertaining to combined estrogen-progestin therapy may therefore not apply to progestin-only therapy. Physician discretion is advised.

General

Effects on ability to drive and use machines

Transient and occasional somnolence or dizziness may occur in some patients 1-4 hours after ingestion of PROGESTERONE, particularly if administered with food. Activities requiring concentration, good attention, good coordination or reflex action should be avoided when the above-mentioned neurological symptoms occur. In most cases, these problems can be avoided by taking the capsules at the recommended times. The 200 mg dosage should be taken at bedtime. The 300 mg dosage should be divided into two doses, 100 mg 2 hours after breakfast and 200 mg at bedtime.

Carcinogenesis and Mutagenesis

Breast Cancer

Available epidemiological data indicate that the use of combined *estrogen plus progestin* by postmenopausal women is associated with an increased risk of invasive breast cancer.

In the *estrogen plus progestin* arm of the WHI trial (conjugated equine estrogens (CEE), 0.625 mg/day plus medroxyprogesterone acetate (MPA) 2.5 mg/day), among 10,000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo). 31

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs. 1.5 cm [0.9], respectively; p=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.[2]

In the *estrogen-alone* arm of the WHI trial (CEE at 0.625 mg/day), there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.[30]

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

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counselling.

Ovarian cancer
Some recent epidemiologic studies have found that the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

Cardiovascular

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.[8, 11, 31] The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women.[28,29]

WHI trial findings
In the combined *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo).[31]

In the estrogen-alone arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD.[30]

HERS and HERS II findings
In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE 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 hormone-treated group than in the placebo group in year 1, but not during the subsequent years.[11]

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.[8]

High Blood Pressure
Women using hormonal replacement therapy (HRT) sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

Endocrine and Metabolism

Glucose and Lipid Metabolism
A worsening of glucose tolerance and lipid metabolism has been observed in a significant percentage of peri- and post-menopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

Women with familial hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally before treatment is started.

Calcium and Phosphorus Metabolism
Because the prolonged use of estrogens, with or without progestins, influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Heme metabolism

Women with porphyria need special surveillance.

Genitourinary

Vaginal Bleeding
Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt diagnostic measures like hysteroscopy, endometrial biopsy or curettage to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Hematologic

Venous Thromboembolism
Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 (34 on combined HRT versus 16 on placebo) more cases of venous thromboembolism, including 8 (16 on combined HRT versus 8 on placebo) more cases of pulmonary embolism.[31]

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 (28 on estrogen therapy versus 21 on placebo) more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.[30]

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition)

and severe obesity (body mass index > 30 kg/m2). The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens with or without progestins should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Hepatic/Biliary/Pancreatic

Jaundice
Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

Liver Function Test
Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests (see DRUG INTERACTIONS, Drug-Laboratory Interactions, Laboratory Tests).

Immune

Systemic lupus erythematosus
Particular caution is indicated in women with systemic lupus erythematosus.

Neurologic

Cerebrovascular Insufficiency
Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis, or loss of consciousness should discontinue medication.
Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be revaluated.

Dementia
Available epidemiological data indicate that the use of combined estrogen plus progestin in women age 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (*estrogen plus progestin* or *estrogen-alone*) reduces the risk of dementia in women aged 65 and over and free of dementia at baseline.[26,27]

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with an intact uterus were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo).[26]

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance.[27]

When data from the *estrogen plus progestin* arm of the WHIMS and the *estrogen-alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 *on estrogen plus progestin* or *estrogen-alone* versus 23 on placebo).[27]

Epilepsy
Particular caution is indicated in women with epilepsy, as estrogens with or without progestins may cause an exacerbation of this condition.

Renal

Fluid Retention
Estrogens, with or without progestins, may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

Special Populations

Pregnant Women
If the patient is exposed to PROGESTERONE capsules during the first 4 months of pregnancy or if she becomes pregnant while taking this drug she should be informed of the potential risks to the fetus.

A case of cleft palate was reported. Additionally rare cases of fetal death (causality not established) have been reported when micronized progesterone was used for unapproved indications.

Cases of hepatocellular disease have been reported rarely in women treated with micronized progesterone during the second and third trimester (see ADVERSE REACTIONS).

Nursing Women
Detectable amounts of progesterone have been identified in the milk of mothers receiving progesterone. The possible effects of progesterone on the nursing infant have not been determined.

Monitoring and Laboratory Tests

Physical Examination

Before PROGESTERONE is administered; the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. 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 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

It is important that patients are encouraged to practice frequent self-examination of the breasts.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See WARNINGS AND PRECAUTIONS regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

Adverse events that could be considered to be possibly associated with micronized progesterone therapy are: breakthrough bleeding, spotting, and menstrual irregularity.

Under the recommended conditions of use (200 mg HS), dizziness, somnolence, cramps or nausea have been reported occasionally.

Fatigue, headache, vertigo, light-headedness or migraine have been reported rarely.

Breast

Breast tenderness may occur with the use of PROGESTERONE.

Other adverse events which are generally attributed to synthetic progestins and which may possibly occur during PROGESTERONE treatment include: chloasma, pruritus, jaundice, rash, fluid retention, mental depression and thrombotic disorders.

The following adverse reactions have been reported with estrogen/progestin combinations in general:

- **Blood and Lymphatic System Disorders**
  Altered coagulation tests (see DRUG INTERACTIONS, Drug-Laboratory Interactions, Laboratory Tests).

- **Cardiac Disorders**
  Palpitations; increase in blood pressure (see WARNINGS AND PRECAUTIONS); coronary thrombosis.

- **Endocrine Disorders**
  Increased blood sugar levels; decreased glucose tolerance.

- **Eye Disorders**
  Neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses.

- **Gastrointestinal Disorders**
  Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating).

- **General Disorders and Administration Site Conditions**
  Fatigue; changes in appetite; changes in body weight; change in libido.

- **Hepatobiliary Disorders**
  Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

- **Musculoskeletal and Connective Tissue Disorders**
  Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

- **Nervous System Disorders**
  Aggravation of migraine episodes; headaches; dizziness; neuritis.

- **Psychiatric Disorders**
  Mental depression; nervousness; irritability.

- **Renal and Urinary Disorders**
  Cystitis; dysuria; sodium retention; edema.

- **Reproductive System and Breast Disorders**
  Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea ; vaginal itching/discharge; dyspareunia; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.

- **Skin and Subcutaneous Tissue Disorders**
  Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.

- **Vascular Disorders**
  Isolated cases of: thrombophlebitis; thromboembolic disorders.

If adverse symptoms persist, the prescription of HRT should be re-considered.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 lists adverse reactions experienced in a double-blind, randomized, parallel-group study that compared the efficacy and safety of micronized progesterone 200 mg and 300 mg with placebo for a duration of treatment of 10 days. Two patients withdrew from the study prior to receiving study drug. The majority of adverse reactions experienced are those resulting from the pharmacological action of progesterone as well as from the onset of withdrawal bleeding. These events include cramping, nausea, abdominal pain and/or bloating and tender or swollen breasts.

Table 1: Adverse Reactions Reported in a 60 Patient Double-Blind, Randomized, Parallel-Group Study [Percentage (%) of Patients Reporting]

	Micronized Progesterone 200mg N = 19	**Micronized Progesterone 300mg N = 20**	**Placebo N = 21**
Cramps	58%	35%	29%
Nausea	5%	15%	10%
Breast Tenderness	5%	10%	19%
Abdominal Discomfort	5%	10%	14%
Dizziness	11%	15%	14%
Tired/Lethargy	21%	20%	14%

Dupont et al conducted a single-blind, randomized, controlled study that compared percutaneous estradiol and oral conjugated estrogens as replacement therapy (with or without micronized progesterone) in sixty-three healthy postmenopausal women for 24 weeks. In this study, serum aldosterone concentrations were slightly elevated in subjects receiving micronized progesterone independent of the form of estrogen therapy administered. The increase in aldosterone was not associated with any clinical symptoms or side effects. There was no significant change in diastolic and systolic blood pressure.[5]

Table 2 lists adverse experiences which were reported in ≥2% of patients (regardless of relationship to treatment) who received cyclic capsules of micronized progesterone, 200 mg daily (12 days per calendar month cycle) with daily 0.625 mg conjugated estrogen, in a multicenter, randomized, double-blind, placebo-controlled clinical trial (Postmenopausal Estrogen and Progestin Interventions (PEPI) Trial) in 875 postmenopausal women. Table 2 also lists adverse experiences reported in the conjugated estrogen-alone group and placebo group of the PEPI trial.

Table 2: Adverse Experiences (≥2%) Reported in an 875 Patient Placebo-Controlled Trial in Postmenopausal Women over a 3-Year Period [Percentage (%) of Patients Reporting]

	Capsules of Micronized Progesterone 200 mg with Conjugated Estrogens 0.625 mg	**Conjugated Estrogens 0.625 mg (only)**	**Placebo**
	(N = 178)	(N = 175)	(N = 174)
Headache	31	30	27
Breast Tenderness	27	16	6
Joint Pain	20	22	29
Depression	19	18	12
Dizziness	15	5	9
Abdominal Bloating	12	10	5
Hot Flashes	11	14	35
Urinary Problems	11	10	9
Abdominal Pain	10	13	10
Vaginal Discharge	10	10	3
Nausea / Vomiting	8	6	7
Worry	8	5	4
Chest Pain	7	4	5
Diarrhea	7	7	4
Night Sweats	7	5	17
Breast Pain	6	6	2
Swelling of Hands and Feet	6	9	9
Vaginal Dryness	6	8	10
Constipation	3	3	2

Post-Market Adverse Drug Reactions

During the marketing of micronized progesterone internationally, cases of hepatocellular liver disease have been reported rarely. Most of these occurred in women treated outside of the approved indications, i. e., during the second and third trimester of pregnancy when premature labour was threatened.

Additional adverse experiences have been observed in women taking progestins in general:

anaphylaxis and anaphylactoid reaction, rash with and without pruritus, confusion, speech disorder, impaired concentration, and hot flashes. Additionally, rare instances of syncope have been reported.

If adverse symptoms persist, the prescription of HRT should be re-considered.

DRUG INTERACTIONS

Overview

Drugs Inducing Liver Enzymes
Preparations inducing liver enzymes (e.g., barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampin) may interfere with the activity of orally administered progestins.

Drugs Inhibiting Liver Enzymes
Metabolism of progesterone capsules by human liver microsomes was inhibited by ketoconazole (IC50 <0.1 microM; ketoconazole is 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.

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Concomitant administration of aminoglutethimide with MPA may significantly reduce the bioavailability of MPA. It is unknown whether this interaction occurs with micronized progesterone.

Drug-Food Interactions

Concomitant food ingestion increased the AUC and C_{max} values of the capsules of micronized progesterone, with no effect on T_{max} relative to a fasting state when administered to postmenopausal women at a dose of 200mg, for information (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Drug-Herb Interactions

It was found that some herbal products (e.g. St-John's wort), which are available as OTC products, might affect metabolism, and therefore, efficacy and safety of estrogen/progestin products. Physicians and other health care providers should be aware of other non-prescription products concomitantly used by the patient, including herbal and natural products, obtained from the widely spread Health Stores.

Drug-Laboratory Interactions

Laboratory Tests
The following laboratory results may be altered by the use of progesterone: levels of gonadotropin, plasma progesterone, and urinary pregnanediol.

The results of certain endocrine and liver function tests may be affected by progestin-containing products:

- impaired glucose tolerance;
- reduced serum folate concentration;
- change in plasma lipoprotein levels.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks. The pathologist should be informed that the patient is receiving HRT therapy when relevant specimens are submitted.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Hormone Replacement Therapy
In general, the dosage of PROGESTERONE is 200 mg daily for the last 14 days of estrogen treatment per cycle (i.e. from day 8 to day 21 for a 28-day cycle, and from day 12 to day 25 for a 30-day cycle). Estrogens should be administered daily at the lowest effective dose. Patients being treated with high dosages of estrogen (equivalent to 1.25 mg conjugated estrogens or higher) should be administered 300 mg daily for the last 12-14 days of estrogen treatment.

The dosage of PROGESTERONE should be proportional to the dosage of estrogen. With adequate adjustment of the dosage of PROGESTERONE, patients should experience either regular withdrawal uterine bleeding or cessation of bleeding (amenorrhea).

Missed Dose

If a patient is treated with 200 mg daily (total dose at bedtime) and she forgets to take this dose, she should take an extra dose of one capsule (100 mg) the following morning and continue taking the 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.

Administration

The 200 mg daily dosage of PROGESTERONE should be taken at bedtime. Patients receiving 300 mg PROGESTERONE daily should take one capsule (100 mg) in the morning and two capsules (200 mg) at bedtime. The morning dose should be taken 2 hours after breakfast.

OVERDOSAGE

Symptoms
The toxicity of progesterone is very low. Symptoms that may occur are: nausea, vomiting, somnolence and dizziness.

Progestin (norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

For management of a suspected drug overdosage, contact your regional Poison Control Center immediately

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PROGESTERONE is an oral dosage form of the naturally occurring steroid; it is chemically identical to progesterone of ovarian origin.

Progestins are used in combination with estrogens to prevent estrogen-induced endometrial hyperplasia and reduce the risk of endometrial carcinoma to that of untreated women.

Clinical Pharmacology

PROGESTERONE is intended for use in women with an intact uterus as an adjunct to estrogen replacement therapy. Progesterone exerts significant anti-proliferative effects on the oestrogenised endometrium and maintains sufficient control of endometrial mitotic activity through suppression of nuclear estradiol receptors, significant reduction in epithelial and stromal DNA synthesis and induction of 17ß-estradiol dehydrogenase and isocitric dehydrogenase activity.

PROGESTERONE has the same effects as natural endogenous progesterone. It reduces mitotic activity in the endometrial glandular cells; the endometrium is transformed like in the physiological cycle sequence. Secession may lead to withdrawal bleeding. PROGESTERONE significantly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomized women. This is of particular significance in cases of prolonged oestrogen therapy during the menopause.

PROGESTERONE acts as slight nitrogen catabolic, but has neutral or very little effect on serum lipids, calcium metabolism, blood pH, and on hormones such as prolactin, estradiol, oestrone. The mineralocorticoid effect of progesterone metabolites is itself largely antagonized by the antimineralocorticoid effect of progesterone.

PROGESTERONE has no oestrous or androgenic effects.

PROGESTERONE acts mainly antioestrogenically at low doses (200 mg / day).

PROGESTERONE administered per os is a physiologic inhibitor of aldosterone and thus increases the sodium excretion rate. A 200 mg dose of micronized progesterone is equivalent to a dose of 25 to 50 mg of spironolactone as an aldosterone inhibitor.

PROGESTERONE has no significant effect on carbohydrate metabolism, even when administered to non-insulin dependent diabetics. PROGESTERONE does not negate the beneficial oral or transdermal estrogen-induced effect on lipoprotein profiles. In general, administration of

PROGESTERONE (with or without estrogen) does not lead to significant changes in systolic and diastolic blood pressure or heart rate in normotensive women.

Administration of PROGESTERONE does not lead to any significant change in renin substrate, even when administered to diabetic patients. Administration of PROGESTERONE in combination with percutaneous estradiol produces a decrease in blood platelet aggregation in perimenopausal women. In combination with oral conjugated estrogens, PROGESTERONE does not negatively affect the balance between the vasoactive prostanoids PGI2 and TxA2.

Pharmacokinetics

Absorption and Distribution

Pharmacokinetic studies indicate that plasma progesterone levels within the luteal range are achieved with peak levels (mean 77.3 nmol/L) at 2-4 hours following oral administration to postmenopausal women of capsules of micronized progesterone 200 mg.

Table 3: Mean Pharmacokinetic parameters in postmenopausal women after five daily doses of capsules of progesterone.

Mean (n = 15) Day 5 Progesterone C_{max} and AUC Values after Administration of progesterone 200 mg and 300 mg Once-Daily		
	Micronized Progesterone Dose (mg/day)	
	200	**300**
C_{max} (nmol/L)	121.2	192.7
AUC_{0-10} (nmol.hr/L)	321.8	558.7

The plasma concentration of progesterone then declines slowly but remains within the range found in the mid-luteal phase for approximately 9 to 12 hours after administration. Plasma progesterone levels remain above baseline 84 hours after administration of the final dosage. Ingestion of food following administration of progesterone significantly increases AUC and C_{max} values, with no effect on T_{max}. Bioavailability (defined as area under the curve, AUC) is linearly related to the dose.

Progesterone concentrations measured in the endometrium after 8 days of treatment with micronized progesterone either 200 mg/day or 300 mg/day are comparable to physiologic levels during the luteal phase even 12 hours after administration. This fact demonstrates the strong retention of this hormone in target tissue, which is responsible for its biological action during 24 hours. Similarly, significant increases in progesterone concentrations occur in breast tissue.

Intestinal absorption is rapid. Micronization of progesterone improves its absorption by the digestive tract by increasing the surface area in contact between the steroid and the mucous membrane.

Metabolism and Excretion

Following administration of micronized progesterone 300 mg, the major inactive metabolite (pregnanediol-3 α glucuronide) and the 2 major active metabolites (17-hydroxyprogesterone, 20 α dihydroprogesterone) show similar plasma profiles to progesterone. Twenty-four hours following oral administration of 200 mg of micronized progesterone to postmenopausal women, 22.8 mg of pregnanediol glucuronide are eliminated in urine. The second major excretion pathway is via the bile and the feces.

Since PROGESTERONE is metabolized primarily by the liver and is excreted mainly in the urine, patients with illness related to the liver and/or kidneys should be monitored closely.

STORAGE AND STABILITY

Store at room temperature (15ºC - 30ºC). Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Capsules 100 mg:

PROGESTERONE is supplied as beige, soft-gelatin, round-shape capsule. It contains a white-beige suspension, which is free from foreign matter. Every capsule has a "100" printed in black ink.

PROGESTERONE capsules are available in HDPE bottles of 100 capsules and blister package of 30 capsules.

Each coated PROGESTERONE capsules contains 100 mg of micronized progesterone and the following non-medicinal ingredients: Ammonium Hydroxide, Butyl Alcohol, Black Iron Oxide, Gelatin, Glycerin, Isopropyl Alcohol, Lecithin, Light Mineral Oil, Purified Water, Propylene Glycol, Shellac Glaze, Sunflower Oil and Titanium Dioxide

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

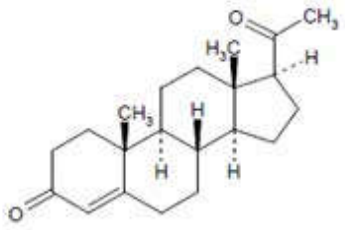
Drug Substance

Proper Name: Progesterone USP

Chemical Name: Pregn-4-ene-3, 20-Dione

Molecular Formula: $C_{21}H_{30}O_2$

Structural Formula:



Molecular Weight: 314.47 g/mol

Physicochemical Properties

Physical Form: White or creamy white crystalline powder

Solubility: Practically insoluble in water; soluble in methanol, ethanol, ethyl acetate; freely soluble in dimethylformamide, dioxane, chloroform, dichloromethane; sparingly soluble in vegetable oils.

CLINICAL TRIALS

Comparative Bioavailability Study

A single center, randomized, double-blind, two-treatment, four-period, full replicate crossover bioequivalence study of PROGESTERONE 100 mg capsules (Sanis Health Inc., Canada) and [Pr]PROMETRIUM® (progesterone) 100 mg capsules (Merck Canada Inc., Canada). The study drugs were administered as a single 200 mg dose (2 x 100 mg) to 40 healthy, postmenopausal female subjects under fasting conditions with 37 subjects completing the four-period study and 40 subjects completing at least three-periods. The results from the measured data include data from 40 subjects and are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Progesterone – Baseline Corrected (200 mg dose: 2 x 100 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_T (pg·h/mL)	12812.2 25386.1 (190.9)	12979.4 24228.1 (187.6)	98.7	88.7 – 109.9
AUC_I (pg·h/mL)	13234.6 26331.5 (190.0)	13315.0 24788.5 (186.5)	99.4	89.4 – 110.5
C_{max} (pg/mL)	2905.8 6842.0 (197.5)	2778.9 5725.2 (187.2)	104.6	88.3 – 123.8
T_{max} § (h)	2.50 (0.66 – 9.00)	2.50 (0.66 – 16.00)		
$T_{½}$ € (h)	10.1 (60.8)	11.0 (59.8)		

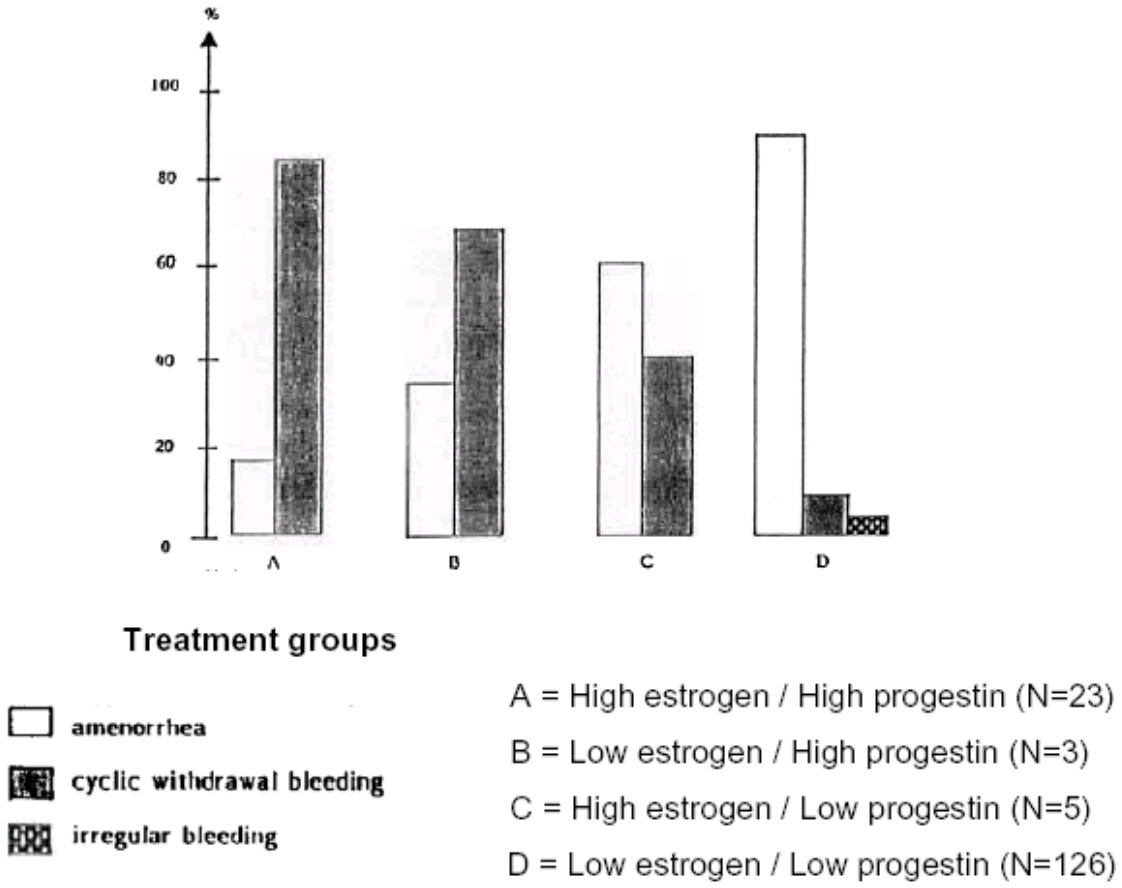
* PROGESTERONE 100 mg capsules (Sanis Health Inc.)
† [Pr]PROMETRIUM® (progesterone) 100 mg capsules (Merck Canada Inc.) and were purchased in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV %) only

A long-term study evaluated the efficacy and safety of micronized progesterone 200 mg and 300 mg to prevent endometrial hyperplasia in postmenopausal women receiving long term Hormone Replacement Therapy (HRT). The study also aimed to identify those characteristics of endometrial morphology that are essential for long term safety in postmenopausal women who are receiving different combinations of estradiol and progesterone over a period of five or more years. Two hundred thirty six (236) women having natural symptomatic menopause and seeking hormone replacement therapy were initiated into the study.

The women were treated with an initial low dose of 1.5 mg percutaneous estradiol, for 21 days out of 28, and 200 mg oral micronized progesterone, given for the last 14 days of estrogen treatment. Within the first 6 months of treatment, the initial progesterone dose was eventually increased to 300 mg in patients willing to have regular withdrawal bleeding and who did not have it with 200 mg per day. The monthly duration of estradiol treatment was prolonged to 25 days out of 28 in the case of recurrence of clinical symptoms during the treatment free week and the monthly duration of oral micronized progesterone treatment was shortened to 10 or 12 days in the case of early uterine bleeding appearing before the end of the course of each cycle of treatment. The 200 mg micronized progesterone dose was given at bedtime. The 300 mg dose was divided into 100 mg taken in the morning and 200 mg at bedtime. The treatment groups were as follow: 126 women received 1.5 mg estradiol plus 200 mg micronized progesterone (Treatment Group A), 3 women received 1.5 mg estradiol plus 300 mg micronized progesterone (Treatment Group B), 5 women received 3 mg estradiol plus 200 mg micronized progesterone (Treatment Group C) and 23 women received 3 mg estradiol plus 300 mg micronized progesterone (Treatment Group D).

Of the 236 women initiated into this study, 79 dropped out during the first 5 years of treatment. The primary reasons for not continuing treatment were the lack of recurrence of initial clinical symptoms after several years of HRT or fear of potential side effects of HRT. These patients were not included in statistical analysis. In the 4 women who developed irregular bleeding while under treatment, a dilation and curettage was performed. The tissue morphology showed benign endometrial polyps in 3 cases and a fourth woman was diagnosed as having a submucosal leiomyoma. None of these four women showed either endometrial hyperplasia or carcinoma. An increased incidence of amenorrhea was seen with the treatment groups (E=estrogen, P=progestin): high E/high P < low E/high P < high E/low P < low E/low P (see also Figure 1).

An inverse relationship was seen for the incidence of withdrawal bleeding. Incidences of irregular bleeding were reported in the low estrogen/low progestin group. The combinations of percutaneous estradiol and micronized progesterone used in this study were sufficient to protect the endometrium from hyperplasia and adenocarcinoma. Administration of oral micronized progesterone (200 mg/day) was sufficient to significantly reduce mitotic activity in the endometrial glandular cells with a maximal reduction noted after a mean of 11 days of progesterone exposure. The progesterone antiproliferative effects (decrease in epithelial mitotic activity) may be separated from other secretory changes (stromal pseudostratification and glandular secretion).



a: 5.7 years was the mean duration of treatment at the time of endometrial biopsy or hysteroscopy.

Figure 1: Bleeding patterns during the last 12 months of the 5.7 years[a] study according to different estradiol/progesterone treatments

A double-blind, randomized, parallel-group study compared the efficacy and safety of micronized progesterone 200 mg and 300 mg with placebo, in the initiation of withdrawal bleeding in patients with secondary amenorrhea. The duration of treatment was 10 days, and the efficacy on withdrawal bleeding was determined over a 16-day period (10 treatment days plus 1 week following the final dose). Efficacy analysis was based on sixty women receiving either micronized progesterone 200 mg (100 mg x 2 capsules + 1 placebo capsule) (19 women), 300 mg (100 mg x 3 capsules) (20 women) or placebo (3 capsules) (21 women), once daily at bedtime. Patients were assessed for withdrawal bleeding from the beginning of treatment up to and including one week following the final dose. Efficacy of micronized progesterone treatment was determined by comparing each of the progesterone groups to the placebo group with respect to the initiation of withdrawal bleeding.

Table 4 summarizes withdrawal bleeding results following treatment in all 3 groups. Ninety percent (90%) (18/20) of the patients in micronized progesterone 300 mg group experienced withdrawal bleeding as compared to 53% (10/19) in micronized progesterone 200 mg group and 24% (5/21) in the placebo group. The proportion of patients experiencing withdrawal bleeding in micronized

progesterone 300 mg group was significantly greater than in the placebo group (one-tailed $p<0.001$); whereas the micronized progesterone 200 mg group was not significantly different from the placebo group (one-tailed $p>0.05$). There was a significant difference between the two treatment groups (two-tailed $p=0.0253$). Approximately twice as many patients in micronized progesterone 300 mg group had withdrawal bleeding as compared to the 200 mg group (90% vs. 53%).

Table 4: Withdrawal Bleeding with Micronized Progesterone and Placebo

	Micronized Progesterone 200mg (N = 19)	**Micronized Progesterone 300mg (N = 20)**	**Placebo (N = 21)**
Patients having withdrawal bleeding	53%	90%	24%
Average number of days until withdrawal bleeding	8.7	10.7	10.4

A single-blind, randomized, controlled study compared oral and percutaneous routes of administration of estrogen, given either with or without micronized progesterone, as HRT for menopause. Criteria of effectiveness included transformation of the endometrium and endocrine profiles. Sixty-three healthy postmenopausal women entered the study. Percutaneous estradiol (2.5 mg) or oral conjugated estrogens (0.625 mg) was administered daily to hysterectomized (31 women) and non-hysterectomized (32 women) women from day 1 to day 25 of a 28-day cycle. Non-hysterectomized women also received 200 mg micronized progesterone on day 12 to day 25 of the 28-day cycle. In all cases, no treatment was administered during days 26 to 28. The duration of treatment was 6 months. Blood samples were obtained from each participant prior to treatment and throughout the replacement therapy. Serum LH, FSH and progesterone were determined. The 32 non-hysterectomized women had endometrial biopsies obtained by curettage before and after 24 weeks of replacement therapy. Morphological evaluation was assessed by light microscopy.

No patients dropped out during this study. Addition of micronized progesterone increased the inhibitory effect of the estrogen preparations on both LH and FSH. Serum progesterone levels fluctuated between 6 and 10 nmoL/L for the day 12 to day 25 period of each cycle, which is characteristic of levels seen during late luteal phases. Serum LH concentrations were lowered to 67, 79, 62 and 67% of their pretreatment concentrations following transdermal estradiol + micronized progesterone, transdermal estradiol alone, oral conjugated estrogens + micronized progesterone and oral conjugated estrogens alone, respectively, while FSH serum levels were respectively decreased to 60, 80, 46 and 57% of pretreatment values. Mitotic activity remained low in all cases after three or more days of micronized progesterone treatment, and no patients showed cystic or glandular hyperplasia. The anti-proliferative endometrial control seen in patients receiving 200 mg micronized progesterone in addition to either estrogen preparation appeared sufficient in all patients. Most of the patients (47%) remained amenorrheic and 34% had regular withdrawal bleeding. Micronized progesterone administration did not influence the activity of 17β-hydroxysteroid dehydrogenase as the conversion of oestrone to estradiol was similar in both groups of women receiving oral conjugated estrogens with or without micronized progesterone.

Lindenfeld et al. evaluated the bleeding patterns with common regimens of HRT using two different progestogens in the Postmenopausal Estrogen and Progestin Interventions Trial (PEPI). A total of

875 women in the PEPI trial took either placebo, conjugated equine estrogen 0.625 mg, conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg in a continuous fashion, or conjugated equine estrogen 0.625 mg daily plus either cyclical MPA 10 mg or cyclical micronized progesterone 200 mg/day for 12 days per month. For 596 patients with a uterus, bleeding days, amounts, and episodes were recoded for 3 years. Conjugated equine estrogens plus micronized progesterone cyclical was associated with fewer excess episodes of bleeding than conjugated equine estrogen plus MPA continuous in the first 6 months. Quantities of bleeding for conjugated equine estrogen plus micronized progesterone cyclical were less than for conjugated equine estrogen plus MPA cyclical through 30 months and for the number of bleeding days through study end. The authors concluded that the bleeding measures for conjugated equine estrogen plus micronized progesterone cyclical showed consistent advantages over those for conjugated equine estrogen plus cyclical MPA in terms of quantity, length, and episodes of bleeding.

Kim et al. study design was to explore the differential threshold of the biologic endpoints of antiproliferation and secretory conversion of the endometrium by different regimes of oral micronized progesterone. Patients were given 300 mg micronized progesterone daily (8:00 am) or twice (8:00 am and 4:00 pm) daily from study days 1 through 14 after estrogen priming for 30 days. The pharmacodynamic effect was examined by endometrial biopsies with regards to histology, glycogen content of glands, ribosomal RNA, and nuclear estrogen receptors in glands, surface epithelium, and stroma. Dose-dependent increases in glandular glycogen, decrease in ribosomal RNA, and decrease in nuclear estrogen receptors were demonstrated. The authors concluded that sustained low concentrations of micronized progesterone probably are sufficient to inhibit endometrial overgrowth and hyperplasia. Ultimately, oral micronized progesterone can induce antiproliferative changes in the human endometrium at doses lower than those required for transformation of the endometrium to a full secretory state.

TOXICOLOGY

The toxicology of micronized progesterone has been studied in rats, rabbits and dogs. The biological effects of micronized progesterone have been demonstrated by increased uterine weight, endometrium development and deciduoma formation in rats and rabbits pretreated with estradiol.

Acute Toxicity

Acute oral toxicity of micronized progesterone has been evaluated in rats and the LD 50 was estimated to be 1,000-2,000 mg/kg in males and 320-400 mg/kg in females.

Subacute Toxicity

Subacute oral toxicity in rats has been studied with daily doses of 40, 100 and 250 mg/kg for 4 weeks as well as daily doses of 5, 15, 45 and 135 mg/kg for 12 weeks. In both subacute studies no mortalities occurred at any treatment level and no toxic or untoward effects were observed at 5, 15, 40 and 45 mg/kg. Signs of sedation, relaxation and coma were seen at higher dose levels (135 and 250 mg/kg) and salivation was seen with a dose of 100 mg/kg. Dose related weight gain was observed in females at the 100 and 250 mg/kg/day dosage. Hematological studies revealed

modest decreases in circulating proteins after 3 months, with inconsistent effects on white blood cell counts. No other significant treatment related effects were observed in clinical signs or histopathology in either study.

In dogs, the subacute oral toxicity of micronized progesterone was studied at daily doses of 50, 125 and 325 mg/kg for 12 weeks. No mortalities were observed at any dose level. Treatment related effects included irritability and sedation in animals receiving 325 mg/kg and serum biochemical alterations at all levels of treatment. Changes in serum cholesterol, lipoproteins, total lipids and electrolyte balance were observed in the treated animals. Target tissue effects of micronized progesterone in treated animals included histopathological findings such as adenosic disease of the breast, ovarian cysts and cystic dysplasia of the endometrium. Treatment related histological changes were not observed in other tissues.

Carcinogenicity

Subcutaneous implantation of progesterone pellets in mice resulted in increases in ovarian granulosa cell tumors and endometrial sarcomas, metaplasia in the endocervical mucosa, squamous cell carcinomas of the cervicovaginal region and hyperplastic nodules of the mammary gland. The findings of tumors in the reproductive tissues of rodents are consistent with that observed with other progestational compounds.

Female beagle dogs, treated with progesterone administered by SC or IM injection for up to four years, developed endometrial and mammary hyperplasia (SC injection) and mammary gland nodules, including two carcinomas (IM injection). The Food and Drug Administration of the United States has concluded that the female Beagle is not an appropriate model for mammary carcinogenicity testing of progestins.

Mutagenicity

Progesterone was negative in vitro for point mutations in the Ames test, in E. coli bacteria, and in the mouse lymphoma forward mutation assay.

Progesterone did not cause mitotic disturbances or chromosome aberrations in Chinese hamster fibroblast cells in culture and did not cause an increase in unscheduled DNA synthesis in hepatocytes from male Fischer 344 rats in culture.

Progesterone was negative in assays for chromosome damage using human female leukocytes, or by the sister chromatid exchange (SCE) assay in human female peripheral blood lymphocytes (HPBL) or in human fibroblast cells.

Chromosome changes were observed in Chinese hamsters receiving SC injections of progesterone for up to four weeks, and in the testes of male mongrel dogs injected IM every other day for six weeks. Since the doses in these studies would have produced blood levels of progesterone in the endogenous range, the toxicological significance of the results is unclear.

Reproduction and Teratology

Administration of progesterone by SC injection to pregnant mice resulted in a decrease in sexual behavior in male offspring with no changes to internal or external genitalia, and an increase in aggressive behavior in female offspring. No abnormalities of internal or external genitalia were observed in the offspring of rats treated with progesterone by SC injection.

No adverse effect on egg development was observed following oral (gavage) administration of progesterone to rabbits three days before or after mating. SC dosing of pregnant rabbits also had no adverse effect on egg development, while SC dosing two days prior to mating induced complete degeneration of eggs. Single SC injection to rabbits before mating did not impair fertility but led to embryonic death by day 4 of gestation.

Administration of progesterone by IM injection to pregnant rhesus monkeys did not cause any adverse effects on pregnancy or on the incidence of anomalies in the offspring.

Human Data
No increased risk of malformations has been reported in several epidemiological, retrospective and prospective studies of women treated with progesterone prior to and during the first trimester of pregnancy.

However, during post marketing use, one case of cleft palate was reported following first trimester use (causality not established). Rare cases of fetal death (causality not established) have also been reported.

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PART III: CONSUMER INFORMATION

PrPROGESTERONE
Progesterone Capsules

This leaflet is part III of a three-part "Product Monograph" published when PROGESTERONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PROGESTERONE. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this CONSUMER INFORMATION carefully before you start taking PROGESTERONE and each time you have your prescription refilled. It contains information on what PROGESTERONE is, when and how to take it, what to look out for, and some information regarding possible risks of hormone replacement therapy obtained from the results of the Women's Health Initiative Study. This information leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment.

ABOUT THIS MEDICATION

What the medication is used for:
PROGESTERONE is approved for use in the following situation:

- In women with an intact uterus (have not had surgery to remove the uterus) who are using estrogen replacement therapy for menopause

Progesterone, as in PROGESTERONE capsules, has a strong influence on the inner lining of the uterus and is used with estrogen therapy during and after menopause. The purpose of using progesterone is to protect the inner lining of the uterus from overgrowth caused by estrogen therapy.

PROGESTERONE should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HRT.

What it does:
The active ingredient in PROGESTERONE capsules is progesterone, a natural female hormone. In healthy women of childbearing age, progesterone is produced by the ovaries each month during the second part of the menstrual cycle. Progesterone plays a role in the monthly shedding of the inner lining of the uterus (endometrium) and the menstrual bleeding that follows.

When it should not be used:
Do not use PROGESTERONE if you:

- Have an allergic or an unusual reaction to progesterone, soya, peanut or to any of the ingredients in PROGESTERONE;
- have liver disease;
- have or have had cancer or abnormalities of the breast or uterus;
- have overgrowth of the lining of the uterus;
- have undiagnosed or unexpected vaginal bleeding;
- are pregnant or suspect you may be pregnant;
- have a history of heart disease (including heart attack) or stroke;
- have migraine headaches;
- have or have had abnormal increase in blood clotting;
- have partially or completely lost vision due to blood vessel disease of the eye

What the medicinal ingredient is:
Micronized progesterone

What the non-medicinal ingredients are:
Ammonium Hydroxide, Butyl Alcohol, Black Iron Oxide, Gelatin, Glycerin, Isopropyl Alcohol, Lecithin, Light Mineral Oil, Purified Water, Propylene Glycol, Shellac Glaze, Sunflower Oil and Titanium Dioxide

What dosage forms it comes in:
Capsules: 100 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial assessed the health benefits and risks of oral combined *estrogen plus progestin* therapy and *estrogen-alone* therapy in postmenopausal women.

The WHI trial indicated increased risk of myocardial infarction (heart attack), stroke, invasive breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women receiving combined estrogen plus progestin.

The WHI trial indicated increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) receiving estrogen alone.

The Women's Health Initiative Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of probable dementia (madness) in postmenopausal women 65 years of age or older.

Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.

- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke or dementia.
- Estrogens with or without progestins should be used at the lowest effective dose and for the shortest period of time possible. Regular medical follow-up is advised.

Breast Cancer
The results of the WHI trial indicated an increased risk of breast cancer in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

The results of the WHI trial indicated no difference in the risk of breast cancer in postmenopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer. In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting hormone replacement therapy.

Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women. You should review technique for breast self-examination with your doctor.

Ovarian cancer
In some studies, the use of estrogen-alone and estrogen plus progestin therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

Stroke and Heart Disease
The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking estrogen alone compared to women taking placebo.

Abnormal Blood Clotting
The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.
The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

Dementia
The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in postmenopausal women age 65 and over taking oral combined estrogen plus progestin compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral estrogen-alone compared to women taking placebo.

BEFORE you use PROGESTERONE talk to your doctor or pharmacist if you:
- have a history of allergy or intolerance to PROGESTERONE or any of its ingredients (see What the medicinal ingredient is/ What the important nonmedicinal ingredients are), or are allergic to soya or peanut or to any other substances or medications;
- have a history of liver disease or jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy;
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer);
- have experienced undiagnosed or abnormal vaginal bleeding;
- have a history of uterine fibroids or endometriosis
- have been diagnosed with lupus
- have a history of heart attack, heart disease or stroke;
- have a history of migraine headache;
- have a personal or family history of blood clots or a personal history of active thrombophlebitis (inflammation of the veins);
- have a partial or complete loss of vision due to blood vessel disease of the eye;
- are pregnant or may be pregnant;
- smoke;
- have a history of high blood pressure;
- have a history of kidney disease, epilepsy (seizures) or asthma;
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus) ;
- have been diagnosed with diabetes;
- have been diagnosed with porphyria (a disease of blood pigment);
- have a history of high cholesterol or high triglycerides;
- have a history of depression.
- have had a hysterectomy (surgical removal of the uterus)

PROGESTERONE may cause some people to feel dizzy or sleepy, 1-4 hours after ingestion of the capsules. Therefore, before you drive or do anything else that requires alertness, make sure you are not experiencing these side effects.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products. Some medications (such as certain anti-seizure medications or antibiotics) may affect how PROGESTERONE capsules work. PROGESTERONE capsules may also affect how your other medicines work.

PROPER USE OF THIS MEDICATION

Usual dose:
Take PROGESTERONE only as directed by your doctor or pharmacist.

Hormone Replacement Therapy for Menopause
The recommended dose is 2 capsules (200 mg) of PROGESTERONE per day for the last 14 days of estrogen treatment each cycle or 3 capsules per day (300 mg) for the last 12-14 days of estrogen treatment each cycle. If you are being treated with 2 capsules (200 mg) a day you should take them both at bedtime. If you are being treated with 3 capsules (300 mg) a day, you should split the daily dose in two parts by taking one capsule in the morning and two at bedtime. PROGESTERONE should be started on the first estrogen cycle. The length of time that you will take PROGESTERONE will depend of the length of time that you are treated with estrogen. PROGESTERONE should be taken as long as you take estrogen and you have an intact uterus (have not had surgery to remove the uterus).

A few days after completing a PROGESTERONE course of 3 capsules daily, the inner lining of the uterus will usually shed. This is accompanied by vaginal bleeding (resembling a normal monthly period). With a dosage of 2 capsules daily, many women will not have such vaginal bleedings, although the lining of the uterus will also be protected against overgrowth.

Overdose:
When someone accidentally takes too much PROGESTERONE, the following symptoms may arise: nausea, vomiting, sleepiness, dizziness, depressive mood, tiredness, acne and hairiness.

If someone has accidentally taken PROGESTERONE or has taken several capsules at once, consult a doctor.

If you think you have taken too much PROGERTERONE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you are being treated with 2 capsules a day (total dose at bedtime) and you forget to take this dose, you should take one capsule the following morning and continue taking the rest of the capsules as prescribed. If you are being treated with 3 capsules a day and you forget to take a morning or evening dose, you should not take the missed dose.

GENERAL THINGS TO REMEMBER:

1. Keep all medication out of the reach of children.
2. This medication has been prescribed only for your current medical condition. Do not use it for other medical problems.
3. Do not allow other people to use your medications and do not use medications meant for other people.
4. Tell any doctor treating you what medications you are taking. Always carry a medical information card stating which medications you are using. This can be very important in case you are involved in an accident.
5. Return unused medications to the pharmacy for safe disposal.
6. Make sure that other people you live with or who look after you read this information.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Depending on the dosage of PROGESTERONE and the sensitivity of the patient, the following side effects are possible: genital bleeding or spotting (minor vaginal bleeding) in between the normal periods (mainly during the first two months); irregular menstrual periods; dizziness or vertigo; sleepiness; abdominal discomfort (cramps, pressure, pain); nausea (urge to vomit); fatigue (tiredness); aggravation of migraine headaches, headaches or depressive mood; light-headedness (feeling faint); breast tenderness/swelling; liver disease.

Side effects observed in women taking progestins in general: a severe allergic reaction which may include hives, itchiness, skin redness, swelling, wheezing, increase heart rate and difficulty breathing; rash with or without itching; rare cases of loss of consciousness; hot flashes; impaired concentration; confusion; swelling; and difficulty with speech.

Other side effects that have been observed with estrogen and progestin combinations in general, but not necessarily with PROGESTERONE treatment are:

- water retention (bloating, swelling);
- overgrowth of the lining of the uterus;
- gallbladder disorder, impaired liver function, jaundice (yellowing of the eyes or skin);
- menstrual cramps;
- vaginal itching/discharge;
- pain during sexual intercourse;
- pain on urination or difficulty urinating;
- premenstrual syndrome (PMS);
- breast tenderness
- inflammation of the bladder;
- brown, blotchy spots on exposed skin (pregnancy mask);
- skin rash, tender red lumps or nodules or other skin reactions;

- loss of hair, hairiness;
- acne;
- palpitations (unpleasant sensation of irregular and/or forceful beating of the heart);
- pain, swelling or redness of the calf or leg which may indicate a blood clot;
- chest pain or shortness of breath which may indicate a blood clot;
- increase in blood pressure;
- depression;
- nervousness;
- irritability;
- visual disturbances, intolerance to contact lenses;
- changes in appetite and body weight;
- change in sexual drive;
- pain in the joints and muscles, usually lasting only 3-6 weeks.
- headache

During your first 2-4 months of HRT, you may experience minor unscheduled vaginal bleeding (at times other than when you would expect a normal period). This is a normal response of your body as it adjusts to the return of estrogen and progesterone to the levels that were seen before menopause. Should unscheduled vaginal bleeding persist, you should consult your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
At any frequency			
Abdominal pain, nausea or vomiting		√	
Breast lump		√	
Crushing chest pain or chest heaviness			√
Pain or swelling in the leg			√
Persistent sad mood.			√
Sharp pain in the chest, coughing blood or sudden shortness of breath			√
Sudden partial or complete loss of vision			√
Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg (any of these, alone or in combination)			√
Unexpected vaginal bleeding		√	
Yellowing of the skin or eyes (jaundice)			√

This is not a complete list of side effects. For any unexpected effects while taking PROGESTERONE, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep out of reach and sight of children
- Store at 15ºC - 30ºC. Protect from light.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/healthcanada/services/drugs-healthproducts/medeffect-canada/adverse-reactionreporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about PROGESTERONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website or contacting Sanis Health Inc. at:

1-866-236-4076
or quality@sanis.com

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