PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

REDDY-PROGESTERONE

Progesterone Capsules

Capsules, 100 mg, For Oral use

Progestin

Manufacturer:
Dr. Reddy's Laboratories, Inc.
Princeton, NJ – 08540 USA

Imported and Distributed by:
Dr. Reddy's Laboratories Canada Inc.
Mississauga, ON L4W 4Y1
CANADA

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS, 1.1 Pediatrics, 1.2 Geriatrics	02/2026
2 CONTRAINDICATIONS	02/2026
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations 4.2 Recommended Dose and Dosage Adjustment, 4.4 Administration	02/2026
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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

REDDY-PROGESTERONE (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.

1.1 Pediatrics

REDDY-PROGESTERONE is not indicated for pediatric use.

1.2 Geriatrics

The evidence of safety and efficacy of progesterone is limited in women over 65 years of age; therefore, progesterone is not indicated in this population.

2 CONTRAINDICATIONS

REDDY-PROGESTERONE (progesterone) is contraindicated in patients with any of the following conditions:

- hypersensitivity to this drug, soya, peanut or to any ingredient in the formulation of the capsule. For a complete listing, see *6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING*.
- liver dysfunction or disease as long as liver function tests have failed to return to normal; see *7 WARNINGS AND PRECAUTIONS.*
- 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).
- 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.
- Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency).
- Porphyria.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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.

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.

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.

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.

See *8 ADVERSE REACTIONS*

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. Health Care Professional discretion is advised.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Pregnancy should be excluded before initiating HRT.

4.2 Recommended Dose and Dosage Adjustment

Hormone Replacement Therapy:

For initiation and continuation of hormone replacement therapy (estrogens and progesterone) in postmenopausal symptoms, the lowest effective dose for the shortest duration should be used (see also *Section 7 WARNINGS AND PRECAUTIONS*).

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

REDDY-PROGESTERONE is not indicated for paediatric use.

4.4 Administration

REDDY-PROGESTERONE is formulated for oral administration and must be swallowed whole. Capsules should not be chewed, crushed nor pierced.

The 200 mg daily dosage of REDDY-PROGESTERONE should be taken at bedtime. Patients receiving 300 mg REDDY-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. Concomitant food ingestion significantly increases the bioavailability of micronised progesterone. See *Section 9.5 DRUG-FOOD INTERACTIONS.*

4.5 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 a 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.

5 OVERDOSAGE

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 the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Capsule, 100 mg progesterone	gelatin, glycerin, soya lecithin, peanut oil, titanium dioxide.

REDDY-PROGESTERONE (micronized progesterone) 100 mg capsules to be taken orally; contain 100 mg micronized progesterone as the active ingredient.

REDDY-PROGESTERONE 100 mg capsule is a round, opaque, white, soft gelatin capsule.

The imprinting Opacode® S-1-277002 Black contains, ammonium hydroxide, black iron oxide, propylene glycol and shellac.

Packaging

REDDY-PROGESTERONE 100 mg progesterone capsules are available in unit dose blister packages, with 30 capsules per package and bottles of 100.

7 WARNINGS AND PRECAUTIONS

See *3 SERIOUS WARNINGS AND PRECAUTIONS BOX.*

General

REDDY-PROGESTERONE is NOT a contraceptive and must only be used in accordance with the indications in Section 1 INDICATIONS

Each Progesterone Soft Capsule 100 mg contains 1 mg soya lecithin and may cause hypersensitivity reactions (urticarial and anaphylactic shock in hypersensitive patients). As there is a possible relationship between allergy to soya and allergy to peanut, patients with peanut allergy should avoid using Progesterone Soft Capsules.
Progesterone Soft Capsules contain highly refined oil, for which the incidence of hypersensitivity is very rare in adults.

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).

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.

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.

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 Health Care Professional 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.

Endometrial hyperplasia & endometrial carcinoma

Estrogen-only HRT increases the risk of endometrial hyperplasia/carcinoma if taken by women with intact uteri. The role of progesterone, when combined with estrogen, is to prevent endometrial hyperplasia/carcinoma in women with intact uteri.

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. 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.

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).

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.

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.

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.

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.

Driving and Operating Machinery
Transient and occasional somnolence or dizziness may occur in some patients 1-4 hours after ingestion of REDDY-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.

Ear/Nose/Throat

Otosclerosis
Estrogens with or without progestins may cause an exacerbation of this condition, therefore caution should be taken.

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 during treatment with HRT. 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.

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.

Uterine leiomyomata
Estrogens with or without progestins may increase the size of pre-existing uterine leiomyomata. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Endometriosis
Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated during the use of estrogens with or without progestins.

Hematologic

Venous Thromboembolism
Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see *section 2 CONTRAINDICATIONS*).

If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g., antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

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.

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.

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 Health Care Professional 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

Liver disease
Particular caution is indicated in women with hepatic hemangiomas or hepatic adenomas as estrogens with or without progestins may cause an exacerbation of these conditions.

Gallbladder diseases
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported. Particular caution is indicated in women with cholelithiasis, as estrogens with or without progestins may cause an exacerbation of this condition.

Jaundice
Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice or deteriorating liver function 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 *section 9 DRUG INTERACTIONS/ Drug-Laboratory Interactions/Laboratory Tests*.

Immune

Angioedema
Estrogens with or without progestins may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

Systemic lupus erythematosus
Particular caution is indicated in women with systemic lupus erythematosus, as estrogens with or without progestins may cause an exacerbation of this condition.

Monitoring and Laboratory Tests

Physical Examination
Before REDDY-PROGESTERONE (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. Examinations should include blood pressure, glucose tolerance, lipid metabolism, and liver function (see *section 7* WARNINGS AND PRECAUTIONS – Endocrine and Metabolism; Cardiovascular; and Hepatic/Biliary/Pancreatic). Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the Health Care Professional.

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

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 reevaluated.

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.

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).

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.

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).

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.

7.1 Special Populations

7.1.1 Pregnant Women

Pregnancy should be excluded before initiating HRT. If pregnancy occurs during the use of progesterone, treatment should be withdrawn immediately.

If the patient is exposed to REDDY-PROGESTERONE (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 post-market following first trimester use (causality not established). Additionally rare cases of fetal death (causality not established) have been reported when progesterone was used for unapproved indications.

Cases of hepatocellular disease have been reported rarely in women treated with progesterone during the second and third trimester (see *8 ADVERSE REACTIONS*).

7.1.2 Breast-feeding

Detectable amounts of progesterone have been identified in the milk of mothers receiving progesterone. REDDY-PROGESTERONE is not recommended during lactation.

7.1.3 Pediatrics

REDDY-PROGESTERONE is not indicated for pediatric use.

7.1.4 Geriatrics

The evidence of safety and efficacy of progesterone is limited in women over 65 years of age; therefore, REDDY-PROGESTERONE is not indicated in this population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

See *7 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 REDDY-PROGESTERONE (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, lightheadedness or migraine have been reported rarely.

Breast tenderness may occur with the use of REDDY-PROGESTERONE.

Other adverse events which are generally attributed to synthetic progestins and which may possibly occur during REDDY-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 *9 DRUG INTERACTIONS/ Drug-Laboratory Interactions /Laboratory Tests).*

- **Cardiac Disorders**
  Palpitations; increase in blood pressure (see *7 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.

8.2 Clinical Trial Adverse 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 2 lists adverse reactions experienced in a double-blind, randomized, parallel-group study that compared the efficacy and safety of 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 2: Adverse Reactions Reported in a 60 Patient Double-Blind, Randomized, Parallel-Group Study [Percentage (%) of Patients Reporting]

	Progesterone 200 mg N=19	Progesterone 300 mg N=19	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 progesterone) in sixty-three healthy postmenopausal women for 24 weeks. In this study, serum aldosterone concentrations were slightly elevated in subjects receiving 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.

Table 3 lists adverse experiences which were reported in ≥2% of patients (regardless of relationship to treatment) who received cyclic 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 3 also lists adverse experiences reported in the conjugated estrogen-alone group and placebo group of the PEPI trial.

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

	Progesterone Capsules 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

8.5 Post-Market Adverse Reactions

During the marketing of 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 post-market adverse experiences without well established cause-relationship have been observed in women taking progesterone:

- **Blood and lymphatic disorders:** Anaemia
- **Cardiac disorders:** Tachycardia
- **Ear and labyrinth disorders:** Tinnitus
- **Eye disorders:** Eye irritation

- **Gastrointestinal disorders:** Abdominal distension, taste disturbances
- **General disorders and administration site conditions:** Malaise, asthenia, chest discomforts, pyrexia
- **Immune system disorder:** Anaphylaxis and anaphylactoid reactions
- **Infection and infestations:** Urinary tract infections, vaginitis
- **Musculoskeletal and connective tissue disorders:** Arthralgia, back pain, limb discomfort, muscle spasms, myalgia
- **Nervous system disorders:** Speech disorder, amnesia, paraesthesia, syncope
- **Psychiatric disorders:** Insomnia, agitation, anxiety, apathy, disorientation, mood swings
- **Reproductive system and breast disorders:** Vaginal haemorrhage, amenorrhoea, metrorrhagia, vulvovaginal discomfort, mastodynia
- **Respiratory, thoracic and mediastinal disorders:** Dyspnoea
- **Skin and subcutaneous tissue disorders:** Hyperhidrosis, urticaria
- **Vascular disorders:** Haemorrhage, hypotension

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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Progestogens may affect the treatment balance of diabetes. The diabetes medicine of patients being treated simultaneously with progestogens may need to be adjusted.

Progesterone may prevent the metabolism of ciclosporin, which increases the concentration ciclosporin concentrations and a risk of toxicity.

Medicines known to induce the hepatic enzyme CYP450-3A4 may increase the metabolism and elimination of progesterone, possibly resulting in a decrease in therapeutic effects and/or changes in uterine bleeding profile. These medicines may include:

- Some antibiotics: rifampicin, rifabutin
- Epilepsy medicines (not valproic acid): phenytoin, phenobarbital, carbamazepine, and topiramate
- Nonnucleoside reverse transcriptase inhibitors: nevirapine, efavirenz
- Sedatives: barbiturates, meprobamate
- Bosentan

Medicines known to inhibit the metabolism of progesterone can lead to an increase in the bioavailability of progesterone, possibly resulting in side effects. These medicines may include:

- Antifungal medicines: fluconazole, itraconazole, ketoconazole, voriconazole
- Antiretroviral medicines: ritonavir, nelfinavir
- Immunosuppressants: tacrolimus

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than those that are hepatic enzyme inducers) on plasma concentrations of synthetic steroids.

9.4 Drug-Drug Interactions

No drug-drug interaction studies have been conducted with progesterone.

9.5 Drug-Food Interactions

Concomitant food ingestion increased the AUC and C_{max} values of progesterone, with no effect on T_{max} relative to a fasting state when administered to postmenopausal women at a dose of 200 mg, for information see *10 CLINICAL PHARMACOLOGY/10.1 Mechanism of Action/10.3 Pharmacokinetics*

9.6 Drug-Herb Interactions

It was found that some herbal products (e.g. St-John's wort, *Hypericum perforatum*), which are available as OTC products, might affect metabolism, and therefore, efficacy and safety of estrogen/progestin products.

Health Care Professionals 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.

9.7 Drug-Laboratory Test 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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

REDDY-PROGESTERONE (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.

10.2 Pharmacodynamics

REDDY-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 estrogenized 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.

REDDY-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. REDDY-PROGESTERONE significantly reduces the oestrogen-induced risk of endometrial hyperplasia in non- hysterectomised women. This is of particular significance in cases of prolonged oestrogen therapy during the menopause.

REDDY-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, oestradiol, oestrone. The mineralocorticoid effect of progesterone metabolites is itself largely antagonized by the antimineralocorticoid effect of progesterone.

REDDY-PROGESTERONE has no oestrous or androgenic effects.

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

REDDY-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 PGI_2 and TxA_2.

10.3 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 progesterone 200 mg.

Table 4: Mean Pharmacokinetic parameters in postmenopausal women after five daily doses of progesterone capsules.

Mean (n=15) Day 5 Progesterone C_{max} and AUC Values after Administration of Progesterone 200 and 300 mg Once-Daily		
	Progesterone Dose (mg/day)	
	200	300
C_{max} (nmol/L)	121.2	192.7
AUC $_{0\text{-}10}$ (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 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 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 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.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature 15°-30°C. Protect from light.
Keep in a safe place out of the reach of children and pets.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

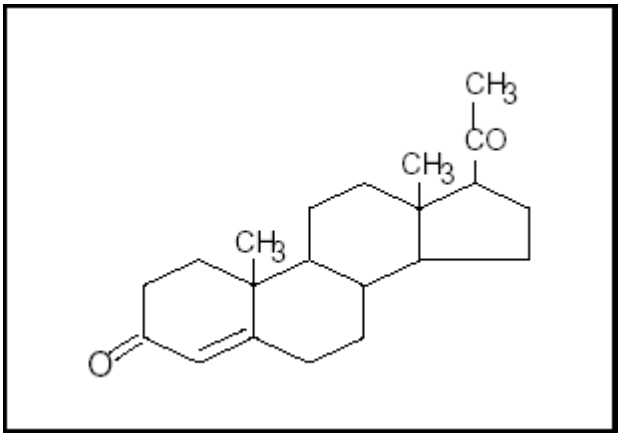
Proper name: Progesterone, U.S.P. micronized

Chemical name: Pregn-4-ene-3,20-dione

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

Molecular mass: 314.47 (g/mol).

Structural formula:



Physicochemical properties:

Physical form: White or creamy white, odorless, crystalline powder.

Solubility: Practically insoluble in water; soluble in alcohol and in dioxane; sparingly soluble in vegetable oils.

Melting range: 126°C - 131°C.

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

Adjunct to postmenopausal estrogen replacement therapy to significantly reduce the risk of endometrial hyperplasia and carcinoma in women with intact uterus

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Moyer 1993	Long-term, open, non-controlled, single-centre observational expanded clinical case report study. (Biopsy done in 1987 or 1988 after a minimum of 5 years of unchanged treatment	Progesterone capsule Oral (Progesterone) • 1.5 mg estradiol plus 200 mg micronized progesterone (last 14 days of estrogen treatment) • 1.5 mg estradiol plus 300 mg micronized progesterone (last 14 days of estrogen treatment) • Treatment Group C: 3 mg estradiol plus 200 mg micronized progesterone • Treatment Group D: 3 mg estradiol plus 300 mg micronized progesterone Minimum 5 years follow up	236	Not specified. All these nonhysterectomized women had amenorrhea for 12 months or more, a plasma E2 level <147 pmol/dL and plasma FSH and LH > 20 IU/L.	Female
Shangold 1991	Phase 3 Single center, prospective, randomized, double blind, placebo controlled study (3 parallel groups).	Progesterone capsule Oral (Progesterone) 200 mg/day 300 mg/day Placebo Duration: 10 days (final interview 2 to 4 weeks after completing medication	60	18 to 52 years old	Female

Dupont 1991	A single-blind, randomized, controlled study	Oral (CEE, 0.625 mg) tablet or percutaneous gel (estrogel 2.5 mg) from day 1 to day 25 - with progesterone capsule Oral (Progesterone) (200 mg) on day 12 to day 25 - without progesterone capsule Oral (Progesterone) Duration: 6 months	63	50 years (37-59)	Female
PEPI **ClinicalTrials.gov ID** NCT00000466 Howard for The Writing Group for the PEPI Trial 1996; Lindenfeld 2002	Phase 3, 3 year multicenter interventional, randomized, double-masked, placebo-controlled clinical trial	- Placebo; - conjugated equine estrogen (CEE), 0.625 mg/day; - CEE, 0.625 mg/day plus cyclic medroxyprogesterone acetate (MPA), 10 mg/day for 12 days per month; - CEE, 0.625 mg/day plus consecutive MPA, 2.5 mg/day; - CEE, 0.625 mg/day plus cyclic micronized progesterone (MP*), 200 mg/day for 12 days a month Duration: 3 years * Progesterone capsule Oral	596	Postmenopausal women, ages 45 to 64	Female
Kim 1996	Controlled, open, parallel group, pilot pharmacodynamic study	Group 1: 300 mg oral micronized progesterone daily Group 2: 300 mg oral micronized progesterone twice daily from study days 1 through 14 after estradiol priming treatment for 30 days Duration: 14 days	12	Group 1: 55.3 (SEM: 2.2). Group 2: 59.5 (SEM: 1.9)	Female

A long-term study evaluated the efficacy and safety of progesterone (micronized progesterone) 200 mg and 300 mg to prevent endometrial hyperplasia in postmenopausal women receiving long term Hormone Replacement Therapy (HRT) (Moyer 1993). 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.

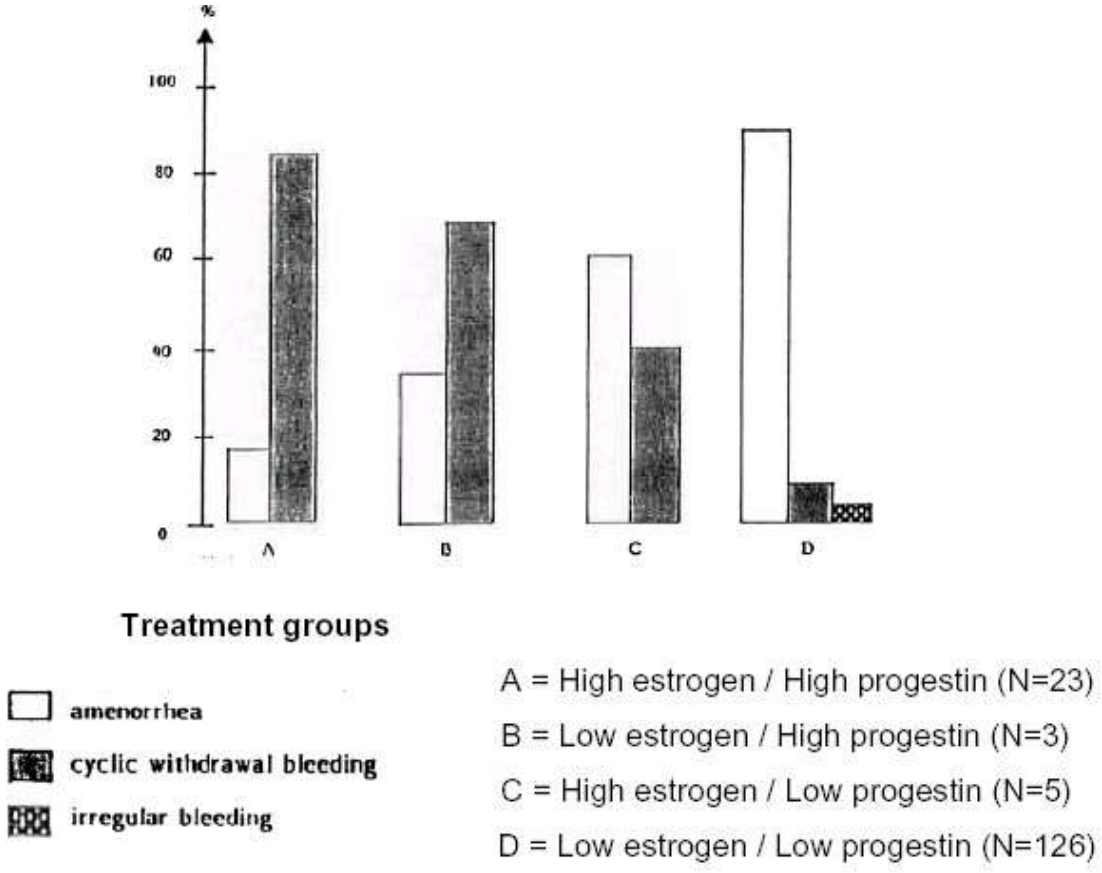
The women were treated with an initial low dose of 1.5 mg percutaneous estradiol, for 21 days out of 28, and 200 mg oral micronized progesterone, given for the last 14 days of estrogen treatment. Within the first 6 months of treatment, the initial progesterone dose was eventually increased to 300 mg 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 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 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).

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



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

A double-blind, randomized, parallel-group study compared the efficacy and safety of progesterone 200 mg and 300 mg with placebo, in the initiation of withdrawal bleeding in patients with secondary amenorrhea (Shangold 1991). 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 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 the progesterone treatment was determined by comparing each of the progesterone groups to the placebo group with respect to the initiation of withdrawal bleeding.

Table 5 summarizes withdrawal bleeding results following treatment in all 3 groups. Ninety percent (90%) (18/20) of the patients in the progesterone 300 mg group experienced withdrawal bleeding as compared to 53% (10/19) in the progesterone 200 mg group and 24% (5/21) in the placebo group. The proportion of patients experiencing withdrawal bleeding in the progesterone 300 mg group was significantly greater than in the placebo group (one- tailed $p<0.001$); whereas the 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 the progesterone 300 mg group had withdrawal bleeding as compared to the 200 mg group (90% vs. 53%).

Table 5: Withdrawal Bleeding with Progesterone and Placebo.

	Progesterone 200 mg N=19	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 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 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 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 + progesterone, transdermal estradiol alone, oral conjugated estrogens + 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 progesterone treatment, and no patients showed cystic or glandular hyperplasia. The anti-proliferative endometrial control seen in patients receiving 200 mg 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.
progesterone administration did not influence the activity of 17β-hydroxysteroid dehydrogenase as the conversion of estrone to estradiol was similar in both groups of women receiving oral conjugated estrogens with or without 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 1996). 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 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 (Lindenfeld 2002). Conjugated equine estrogens plus 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 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.

As part of the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, a study by Judd Howard L. et al. was conducted and aimed to examine the effects of hormone replacement therapy on the endometrial histology of postmenopausal women. The research was conducted on 596 women aged 45 through 64 years without contraindication to hormone therapy. Histology of endometrium were collected at baseline, annual or unscheduled visits by biopsy, curettage or hysterectomy. The results showed that women assigned to estrogen alone had a higher likelihood of developing various types of endometrial hyperplasia compared to those given placebo. However, women administered one of the three estrogen plus progestin regimens had hyperplasia rates that were not significantly different compared to those given placebo. In conclusion, the study found that daily administration of conjugated equine estrogens (CEE) at a dosage of 0.625 mg increased the risk of endometrial hyperplasia. However, combining CEE with cyclic or continuous medroxyprogesterone acetate (MPA) or cyclic micronized progesterone (MP) helped protect the endometrium from hyperplastic changes associated with estrogen-only therapy.

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 progesterone (Kim 1996). Patients were given 300 mg 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 progesterone probably are sufficient to inhibit endometrial overgrowth and hyperplasia. Ultimately, oral 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.

14.2 Comparative Bioavailability Studies

A blinded, balanced, randomized, two-treatment, four-period, two-sequence, single dose, full replicate, oral bioequivalence study of REDDY-PROGESTERONE (Dr. Reddy's Laboratories, Inc.) and PROMETRIUM® (Merck Canada Inc.,) was conducted in healthy, adult, human males and post-menopausal female subjects under fasting conditions. Comparative bioavailability data from 58 subjects that were included in the statistical analysis are presented in the following table:

Progesterone [Baseline Corrected Data] (1 x 100 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (pg·h/mL)	5750.7 13986.4 (274.2)	6117.9 18845.9 (286.0)	94.0	83.1-106.3
AUC_I (pg·h/mL)	6240.0 15043.8 (270.4)	7052.6 21618.4 (285.2)	88.5	80.7-97.0
C_{MAX} (pg/mL)	1521.6 3619.9 (259.0)	1741.0 5834.4 (275.8)	87.4	76.7-99.5
T_{MAX}[3] (h)	1.67 (0.67-10.00)	2.00 (0.67-10.00)		
$T_{½}$[4] (h)	7.15 (65.7)	6.82 (62.2)		

[1] REDDY-PROGESTERONE (progesterone) capsules, 100 mg (Dr. Reddy's Laboratories, Inc.)
[2] PROMETRIUM® (progesterone) capsules, 100 mg (Merck Canada Inc.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %) only

15 NON-CLINICAL 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.

General toxicology

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.

Genotoxicity

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.

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.

Reproductive and Developmental Toxicology

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.

17 SUPPORTING PRODUCT MONOGRAPH

1. PrPROMETRIUM Capsules, 100 mg, submission control 295264, Product Monograph, Organon Canada Inc. (JUL 17, 2025)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

℞ REDDY-PROGESTERONE
Progesterone Capsules

Read this carefully before you start taking **REDDY-PROGESTERONE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **REDDY-PROGESTERONE**.

Serious Warnings and Precautions

In postmenopausal women taking estrogen with progestin, there is an increased risk of:

- Heart attack
- Stroke (bleeding or blood clot in the brain),
- Breast cancer,
- Pulmonary emboli (blood clots in the lungs),
- Deep vein thrombosis (blood clots in the deep veins of the leg or arm). And
- Dementia (in women 65 years or older)

In postmenopausal women taking estrogen-alone who had prior surgery to remove the uterus (called a hysterectomy), there is an increased risk of:

- Stroke (bleeding or blood clot in the brain), and
- Deep vein thrombosis (blood clots in the deep veins of the leg or arm)

Therefore, you should highly consider the following:

- Estrogens with or without progestins should not be used for the prevention of heart disease, 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.

What is REDDY-PROGESTERONE used for?

REDDY-PROGESTERONE is used with estrogen replacement therapy to help treat symptoms of menopause. It helps reduce the risk of:

- endometrial hyperplasia (thickening of the uterus lining)
- uterine cancer

REDDY-PROGESTERONE is intended for women with an intact uterus (has not been removed by surgery).

How does REDDY-PROGESTERONE work?
The active ingredient in REDDY-PROGESTERONE capsules is progesterone, a natural female hormone. In women of childbearing age, progesterone plays a role in the monthly shedding of the inner lining of the uterus (endometrium) and the menstrual bleeding that follows. REDDY-PROGESTERONE helps protect the inner lining of the uterus from overgrowth caused by estrogen therapy during and after menopause.

What are the ingredients in REDDY-PROGESTERONE?

Medicinal ingredients: progesterone

Non-medicinal ingredients: gelatin, glycerin, soya lecithin, peanut oil, titanium dioxide.

The imprinting Opacode® S-1-277002 Black contains, ammonium hydroxide, black iron oxide, propylene glycol and shellac.

REDDY-PROGESTERONE comes in the following dosage forms:

Capsules. Each capsule contains 100 mg (milligrams) of progesterone.

Do not use REDDY-PROGESTERONE if you:

- Have an allergic or an unusual reaction to progesterone, soya, peanut or to any of the ingredients in REDDY-PROGESTERONE;
- Have liver disease;
- Have or have had hormone dependent cancers, like cancer 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 or have had blood clotting problems or disorders;
- Have porphyria (a disorder that affects how your body makes hemoglobin).
- Have partially or completely lost vision due to blood vessel disease of the eye.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REDDY-PROGESTERONE. Talk about any health conditions or problems you may have, including if you:

- have a history of liver disease, liver tumors, 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, abnormal mammograms, 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 been diagnosed with hearing loss due to otosclerosis;
- have been diagnosed with gallstones;

- have been told that you have a condition called hereditary angioedema or if you have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage), or digestive tract have a history of heart conditions;
- have a personal or family history of blood clots or a personal history of active thrombophlebitis (inflammation of the veins);
- are breastfeeding or planning to breastfeed;
- 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 a history of high cholesterol or high triglycerides;
- have a history of migraine headaches;
- have a history of depression;
- have had a hysterectomy (surgical removal of the uterus).

Other warnings you should know about:

Breast Cancer

- Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer.
- There is an increased risk of breast cancer in post-menopausal women taking combined estrogen plus progestin.
- You may also have an increased risk of breast cancer if you have:
  - a family history of breast cancer or have had breast lumps, breast biopsies or abnormal mammograms (breast x-rays);
  - never had a baby before or had your first full-term pregnancy at an older age;
  - you are overweight;
  - you started menstruating at an early age.

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

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

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

There is increased risk of stroke and coronary heart disease in post-menopausal women taking combined estrogen plus progestin.

Abnormal Blood Clotting
There is an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined estrogen plus progestin.

You should discuss risk factors for blood clots with your Health Care Professional since blood clots can be life-threatening or cause serious disability. The risk of blood clots also increases with:

- age,
- family history of blood clots,
- smokers,
- patients that 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.

Dementia
The Women's Health Initiative Memory Study (WHIMS) showed an increased risk of dementia (loss of memory and intellectual function) in postmenopausal women age 65 and over taking oral combined estrogen plus progestin.

Driving and Operating Machinery
REDDY-PROGESTERONE may cause some people to feel dizzy or sleepy, 1-4 hours after ingestion of the capsules. This is more likely if REDDY-PROGESTERONE is taken with food. Do not drive or do anything requiring alertness until you know how REDDY-PROGESTERONE affects you.

Medical Testing
Your Health Care Professional will need to order medical tests before and during your treatment. This will help determine if it is safe for you to continue taking REDDY-PROGESTERONE. These tests include:

- Blood pressure.
- Breast and pelvic exam.
- Pap smear.
- Mammogram.
- Blood glucose.
- Calcium.
- Triglycerides.
- Cholesterol.
- Liver function test.

You should schedule a follow-up with your Health Care Professional within 3-6 months after starting REDDY-PROGESTERONE. You should schedule an appointment with your Health Care professional at least once a year while you are taking REDDY-PROGESTERONE. You should regularly talk with your Health Care Professional about whether you still need treatment with HRT.

Vaginal Bleeding
A few days after completing a REDDY-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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with REDDY-PROGESTERONE:

- anticonvulsant medicines used to prevent seizures, such as phenobarbital, carbamazepine, phenytoin
- antiviral drugs, used to treat viral infections, such as ritonavir and efavirenz
- antifungal drugs, used to treat fungal infections, such as fluconazole, itraconazole, ketoconazole, voriconazole
- bosentan, used to treat high blood pressure
- rifampicin and rifabutin, antibiotics used to treat bacterial infections
- sedatives, such as barbiturates and meprobamate
- tacrolimus, used in organ transplants
- topiramate, used to treat epilepsy and migraines
- some herbal products, such as St. John's wort, used to treat depression

REDDY-PROGESTERONE may interfere with certain medical tests. This may continue for 2-4 weeks after you stop taking REDDY-PROGESTERONE. Tell your Health Care Professional that you are taking REDDY-PROGESTERONE when they order any tests for you.

How to take REDDY-PROGESTERONE:

- Follow the instructions given by your Health Care Professional.
- Capsules of REDDY-PROGESTERONE should be taken by mouth and swallowed whole with a glass of water.
- Do not crush, do not pierce the REDDY-PROGESTERONE capsules.
- Do not take with food. If you are taking REDDY-PROGESTERONE in the morning, wait 2 hours after breakfast before taking your dose.

Usual adult dose:

Your Health Care Professional will adjust your dose based on how much estrogen you are taking.

200 mg daily: Take two capsules (200 mg) in the evening before bed. This dose should be taken for the last 14 days of your estrogen treatment each cycle. This means days 8 to 21 for a 28 day cycle or day 12 to 25 on a 30 day cycle.

300 mg daily: Take one capsule (100 mg) in the morning and two capsules (200 mg) in the evening before bed. This dose should be taken for the last 12-14 days of your estrogen treatment each cycle.

Overdose:

If you take too much REDDY-PROGESTERONE (progesterone), you may experience the following symptoms: nausea, vomiting, sleepiness, dizziness, depressive mood, tiredness, acne and hairiness.

If you think you, or a person you are caring for, have taken too much REDDY-PROGESTERONE, contact a healthcare professional, hospital emergency department, regional poison control center or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you are taking 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 taking 3 capsules a day and you forget to take a morning or evening dose, you should not take the missed dose.

What are possible side effects from using REDDY-PROGESTERONE?

These are not all the possible side effects you may feel when taking REDDY-PROGESTERONE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects of REDDY-PROGESTERONE:

- breast tenderness/swelling/pain;
- dizziness or vertigo;
- fatigue (tiredness);
- genital bleeding or spotting (minor vaginal bleeding) in between the normal periods (mainly during the first two months);
- headaches or depressive mood;
- irregular menstrual periods;
- lightheadedness (feeling faint);
- nausea (urge to vomit), cramps;
- sleepiness, insomnia;

Side effects observed in women taking progestins in general:

- darkening of skin in patches;
- rash with or without itching;
- swelling, bloating from water retention;

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

- acne;
- changes in appetite and body weight;
- change in sexual drive;
- inflammation of the bladder;
- increase in blood pressure;
- irritability;
- loss of hair, hairiness;
- menstrual cramps;
- nervousness;
- overgrowth of the lining of the uterus;

- pain during sexual intercourse;
- palpitations (unpleasant sensation of irregular and/or forceful beating of the heart);
- pain in the joints and muscles, usually lasting only 3-6 weeks;
- pain on urination or difficulty urinating;
- premenstrual syndrome (PMS);
- skin rash, tender red lumps or nodules or other skin reactions;
- vaginal itching/discharge;
- intolerance to contact lenses.

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 Health Care Professional.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Abdominal pain, Abdominal distension, Nausea	√		
UNCOMMON			
Jaundice: Yellowing of the skin or eyes, dark urine, light coloured stool, itching all over your body			√
Unexpected vaginal bleeding Abnormal withdrawal bleeding		√	
Mood disorder: Agitation, Anxiety, Apathy, Depression, Disorientation, Mood swings, Nervousness			√
UNKNOWN			
Breast abnormalities (including breast cancer): Breast lump		√	
Deep vein thrombosis (blood clot in the deep veins of the leg or arm): pain or swelling in the leg/inflamed vein			√
Heart attack, heart disease: Crushing chest pain or chest heaviness, jaw, left arm, between the shoulder blades or upper abdomen, shortness of breath, dizziness, fatigue, lightheadedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat, lack of			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
appetite, nausea, swelling in ankles, legs and feet, cough, fluid retention			
Pulmonary embolism (blood clot in the lung): sharp pain in the chest, coughing blood or sudden shortness of breath			√
Severe allergic reaction: hives, itchiness, skin redness, swelling, wheezing, increase heart rate and difficulty breathing			√
Stroke (bleeding or blood clot in the brain): Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness as per in an arm or leg			√
Sudden partial or complete loss of vision			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

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 (canada.ca/drug-device-reporting) 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.

Storage:
The capsules should be stored at controlled room temperature between 15°C and 30°C. Protect from light. Keep in a safe place out of the reach of children and pets.

If you want more information about REDDY-PROGESTERONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.drreddys.com; or by calling 1-855-845-1739.

This leaflet was prepared by Dr. Reddy's Laboratories Inc.

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