

COMPLETE PRESCRIBING INFORMATION

Pr **PREMARIN**[®] Vaginal Cream
(Conjugated Estrogens, C.S.D.)

0.625 mg/g

ESTROGENIC HORMONES

[®] Pfizer Canada ULC
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Premarin® Vaginal Cream
(Conjugated Estrogens CSD, 0.625 mg/g)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
vaginal	conjugated estrogens vaginal cream 0.625 mg/g	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Premarin® Vaginal Cream is indicated in the treatment of atrophic vaginitis, dyspareunia, and kraurosis vulvae.

PREMARIN® VAGINAL CREAM HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS.

Premarin® Vaginal Cream should be prescribed with an appropriate dose of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma

Geriatrics (> 65 years of age): See above indications.

Pediatrics (< 16 years of age): Premarin® Vaginal Cream is not indicated for use in children.

CONTRAINDICATIONS

Premarin® Vaginal Cream is contraindicated in the following conditions:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. 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.
- Known or suspected estrogen-dependent malignant neoplasia (e.g. endometrial cancer).

- Endometrial hyperplasia.
- Known, suspected, or past history of breast cancer.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy (see WARNINGS AND PRECAUTIONS, Special populations, Pregnant women).
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis.
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Partial or complete loss of vision due to ophthalmic vascular disease.
- Known thrombophilic disorders (e.g., protein C, protein S OR antithrombin deficiency); prothrombin mutation or anticardiolipin antibodies).
- Migraine with or without aura.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *myocardial infarction* (MI), *stroke*, *invasive breast cancer*, *pulmonary emboli* 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 (mean age 63.6 years) 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.

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.
- 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.

General

For the treatment of postmenopausal symptoms, Hormone replacement therapy (HRT) should only be initiated for symptoms/conditions that are consistent with the indications (see INDICATIONS AND CLINICAL USE). In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risks.

Combined Estrogen and Progestin Therapy:

There are additional and/or increased risks that may be associated with the use of combination estrogen-plus-progestin therapy compared with using estrogen-alone regimens. These include an increased risk of myocardial infarction, pulmonary embolism, invasive breast cancer and ovarian cancer.

Systematic absorption may occur with the use of Premarin® Vaginal Cream. Warnings and precautions associated with oral Premarin® treatment should be taken into account.

Latex Condoms

NOTE: Preliminary studies conducted by the Health Products and Food Branch have demonstrated that Premarin® Vaginal Cream may react with the latex rubber of certain mechanical barrier devices used for prevention of sexually transmitted diseases and pregnancy (diaphragms and condoms). In additional studies, Premarin® Vaginal Cream has been shown to weaken latex condoms. The potential for Premarin® Vaginal Cream to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber should be considered.

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, 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, 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 not be given to women with existing breast cancer or those with a previous history of the disease (see **CONTRAINDICATIONS**).

There is a need for caution in prescribing estrogens 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.

Endometrial hyperplasia & endometrial carcinoma

The use of unopposed estrogens has been associated with an increased risk of endometrial hyperplasia/carcinoma. Estrogen should be prescribed with an appropriate dosage of a progestin for women with intact uteri or hysterectomized women with a history of residual endometriosis in order to prevent endometrial hyperplasia/carcinoma (see **WARNINGS AND PRECAUTIONS, Endometriosis**).

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold or greater than in non-users and appears to be dependent on duration of treatment and on estrogen dose. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five years or more, and this risk has been shown to persist for at least 8 to 15 years after ERT is discontinued. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer (see **WARNINGS AND PRECAUTIONS, General**).

Clinical surveillance of all women taking combined estrogen plus progestin HRT is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Ovarian cancer

In some epidemiologic studies, the use of estrogen therapy, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer.

Cardiovascular

Cardiovascular risk

ERT has been reported to increase the risk of stroke and deep venous thrombosis (DVT).

Risk factors for cardiovascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) should be managed appropriately.

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.

Patients who are at risk of developing migraines with aura may be at risk of ischemic stroke and should be kept under careful observation.

Should a stroke occur or be suspected, Premarin® Vaginal Cream should be discontinued immediately.

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 oral 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.

Blood pressure

Women using hormone replacement therapy 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.

Caution should be exercised in patients with pre-existing hypertriglyceridemia since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this population.

Heme metabolism

Women with porphyria need special surveillance.

Estrogens should be used with caution in individuals with pre-existing severe hypocalcemia.

Calcium and phosphorus metabolism

Because the prolonged use of estrogens 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.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients who require thyroid hormone replacement therapy and who are also taking estrogen may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range (see **Drug-Laboratory Test Interactions**).

Genitourinary

Endometriosis

Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

Uterine Leiomyomata

Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Vaginal bleeding

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures 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 oral *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.

In the oral *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 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), severe obesity (body mass index > 30 kg/m²) and systemic lupus erythematosus. 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, Premarin[®] Vaginal Cream should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, Premarin[®] Vaginal Cream 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 disorders

Patients who have previously had liver disorders such as liver adenoma should be closely supervised as this condition may recur or be aggravated during treatment with Premarin[®] Vaginal Cream.

Gallbladder diseases

A 2 to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

Hepatic hemangiomas

Particular caution is indicated in women with hepatic hemangiomas, as HRT 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 develops during treatment, the treatment should be discontinued and appropriate investigations carried out. Estrogens may be poorly metabolized in patients with impaired liver functions.

Liver function tests

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 **Monitoring and Laboratory Tests**.

Immune

Systemic lupus erythematosus

Particular caution is indicated in women with systemic lupus erythematosus, as HRT may cause an exacerbation of this condition.

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

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.

Ophthalmologic: If visual abnormalities develop: Discontinue Premarin® Vaginal Cream pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, Premarin® Vaginal Cream should be withdrawn. Retinal vascular thrombosis has been reported in patients receiving estrogens with or without progestins (see **WARNINGS AND PRECAUTIONS, Hematologic, *Venous thromboembolism***).

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 (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline.

It is unknown whether these findings apply to younger postmenopausal women (see **Special Populations, Geriatrics**).

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with intact uteri 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 HRT may cause an exacerbation of this condition.

Ear/Nose/Throat

Otosclerosis

Estrogens should be used with caution in patients with otosclerosis.

Psychiatric

Depression

Patients who are taking progestogens and have a history of depression should be observed. If the depression occurs to a serious degree, the drug should be discontinued.

Renal

Fluid retention

Estrogens may cause fluid retention.

Therefore, particular caution is indicated in cardiac, 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: Premarin® Vaginal Cream is contraindicated during pregnancy (see CONTRAINDICATIONS). If pregnancy occurs during medication with PREMARIN treatment should be withdrawn immediately.

Nursing Women: Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving the drug. Where an assessment of the risk to benefit ratio suggests the use of this product in nursing women is unfavourable, formula feeding should be substituted for breast feeding.

Pediatrics (< 16 years of age): Premarin® Vaginal Cream is not indicated for use in children. Safety and effectiveness in pediatric population have not been established. Estrogen treatment of prepubertal girls induces premature breast development and vaginal cornification, and may induce uterine bleeding.

Since large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, hormonal therapy should not be started before epiphyseal closure has occurred in order not to compromise final growth.

Geriatrics (> 65 years of age): The estrogen-alone substudy of the Women's Health Initiative (WHI) reported an increased risk of stroke compared with placebo in postmenopausal women 65 years of age or older (see WARNINGS AND PRECAUTIONS, Cardiovascular, and CLINICAL TRIALS).

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Premarin[®] Vaginal Cream to determine whether those over 65 years of age differ from younger subjects in their response to Premarin[®] Vaginal Cream.

Information for Patients

No studies on the effect of ability to drive or use machines have been performed.

Monitoring and Laboratory Tests

Before Premarin[®] Vaginal Cream is administered, the patient should have a complete physical examination including blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests. Before starting treatment pregnancy should be excluded. Periodic check-ups and careful benefit/risk evaluations should be undertaken in women treated with ERT/HRT therapy. The first follow-up examination should be done within three to six months of initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals of at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

Mammography examinations should be scheduled based on patient age, risk factors and prior mammogram results.

The importance of regular self-examination of the breasts should be discussed with the patient.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See **Warnings/Precautions** regarding potential induction of malignant neoplasia and other adverse effects similar to those observed with oral contraceptives.

The following additional adverse reactions have been reported with conjugated estrogens vaginal cream or are undesirable effects associated with ET/HT:

Blood and lymphatic system disorders

Altered coagulation tests (see **WARNINGS AND PRECAUTIONS**, Drug-Laboratory Tests Interactions).

Cardiac disorders

Palpitations; increase in blood pressure (see **WARNINGS AND PRECAUTIONS**); coronary thrombosis, pulmonary embolism, venous thrombosis, myocardial infarction.

Endocrine disorders

Increased blood sugar levels; decreased glucose tolerance, precocious puberty.

Eye disorders

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

Gastrointestinal disorders

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating), pancreatitis; ischemic colitis.

General disorders and administration site conditions

Fatigue; changes in appetite; changes in body weight; changes in libido, aggravation of porphyria, hypocalcemia (in patients with pre-existing conditions of hypocalcemia), angioedema, hypersensitivity, anaphylactic/anaphylactoid reactions, increased triglycerides.

Hepatobiliary disorders

Gallbladder disorder; cholestatic jaundice, asymptomatic impaired liver function.

Musculoskeletal and connective tissue disorders

Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur, arthralgia, leg cramps.

Neoplasms, benign

Fibrocystic breast changes; enlargement of hepatic hemangiomas; growth potentiation of benign meningioma.

Nervous system disorders

Aggravation of migraine episodes; headaches; migraines, dizziness; cerebrovascular accident/stroke; exacerbation of chorea, neuritis.

Psychiatric disorders

Mental depression; nervousness; irritability, mood disturbances, dementia.

Renal and urinary disorders

Cystitis-like syndrome; dysuria; sodium retention; edema.

Reproductive system and breast disorders

Abnormal uterine bleeding; change in menstrual flow; dysmenorrhea/pelvic pain; 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, galactorrhea, breast discharge, amenorrhea, increase in size of uterine leiomyomata, vaginitis, application site reactions of vulvovaginal discomfort including burning, irritation and genital pruritus, vaginal candidiasis; leukorrhea.

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, allergic reactions and rashes, generalized rash, urticaria, pigmentation of the skin, pruritis.

Vascular disorders

Isolated cases of: thrombophlebitis; thromboembolic disorders.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug 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.

Low Dose Regimen

In a 12-week, randomized, double-blind, placebo-controlled trial of conjugated estrogens vaginal cream [Premarin Vaginal Cream (PVC)], a total of 423 postmenopausal women received at least 1 dose of study medication and were included in all safety analyses: 143 women in the PVC-21/7

treatment group (0.5 g PVC daily for 21 days, then 7 days off), 72 women in the matching placebo treatment group; 140 women in the PVC-2x/wk treatment group (0.5 g PVC twice weekly), 68 women in the matching placebo treatment group. A 40-week, open-label extension followed, in which a total of 394 women received treatment with PVC, including those subjects randomized at baseline to placebo. In this study, there were no statistically significant differences in adverse reactions between PVC and placebo. The most common adverse drug reactions $\geq 1\%$ are shown below (Table 1).

Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Drug Reactions $\geq 1\%$				
Body System ^a Adverse Event	Treatment			
	PVC 21/7 N= 143 (%)	Placebo 21/7 N = 72 (%)	PVC 2x/wk N = 140 (%)	Placebo 2x/wk N= 68 (%)
BODY AS A WHOLE				
Abdominal Pain	11 (7.7)	2 (2.8)	9 (6.4)	6 (8.8)
CARDIOVASCULAR SYSTEM				
Hypertension	2 (1.4)	2 (2.8)	5 (3.6)	0
Migraine	2 (1.4)	0	0	2 (2.9)
DIGESTIVE SYSTEM				
Abdominal Distension	2 (1.4)	1 (1.4)	2 (1.4)	1 (1.5)
Nausea	5 (3.5)	4 (5.6)	3 (2.1)	4 (5.9)
Vomiting	3 (2.1)	2 (2.8)	3 (2.1)	3 (4.4)
METABOLIC AND NUTRITIONAL				
Peripheral Edema	2 (1.4)	0	0	0
Weight Gain	3 (2.1)	1 (1.4)	1 (0.7)	0
MUSCULOSKELETAL SYSTEM				
Arthralgia	4 (2.8)	5 (6.9)	5 (3.6)	4 (5.9)
SKIN AND APPENDAGES				
Pruritus	3 (2.1)	1 (1.4)	5 (3.6)	0
Rash	3 (2.1)	1 (1.4)	5 (3.6)	0
UROGENITAL SYSTEM				
Breast Pain	8 (5.6)	2 (2.8)	4 (2.9)	0
Cystitis	1 (0.7)	1 (1.4)	2 (1.4)	1 (1.5)
Leukorrhea	3 (2.1)	2 (2.8)	4 (2.9)	6 (8.8)
Metrorrhagia	3 (2.1)	2 (2.8)	0	1 (1.5)
Vaginal Hemorrhage	1 (0.7)	1 (1.4)	2 (1.4)	2 (2.9)
Vaginitis	8 (5.6)	3 (4.2)	7 (5.0)	3 (4.4)
Vulvovaginitis	0	1 (1.4)	2 (1.4)	0
a. Body system totals for the No. of Patients are not necessarily the sum of the individual adverse events since a patient may report two or more different adverse events in the same body system.				

Other Clinical Trial Adverse Drug Reactions (<1%)

The following adverse events were reported at an incidence of <1% for Premarin Vaginal Cream regardless of drug relationship.

Body As A Whole: Carcinoma; Chills; Cyst; Fever; Injection Site Pain

Cardiovascular System: Cardiovascular Physical; Hemorrhage; Palpitation; Tachycardia

Digestive System: Cheilitis; Cholecystitis; Cholelithiasis; Colitis; Eructation; Esophagitis; Gastritis; Gingivitis; Increased Appetite; Oral Moniliasis; Periodontal Abscess; Tenesmus

Metabolic And Nutritional: Hyperglycemia; Hyperlipemia

Musculoskeletal System: Bone Disorder; Muscle Spasms; Musculoskeletal Stiffness

Nervous System: Agitation; Attention Deficit/Hyperactivity; Confusion; Hostility; Memory Impairment

Respiratory System: Pleural Disorder; Sputum Increased

Skin And Appendages: Alopecia; Hair Disorder; Herpes Simplex; Herpes Zoster; Lichenoid Dermatitis; Night Sweats; Sunburn; Urticaria

Special Senses: Dry Eyes; Ear Disorder; Eye Pain; Lacrimation Disorder

Urogenital System: Breast Disorder; Endometrial Disorder; Genital Edema; Hematuria; Urethral Pain; Urinary Incontinence; Urine Abnormality; Uterine Fibroids Enlargement

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

Post-Marketing Adverse Drug Reactions

The following adverse reactions have been reported with Premarin[®] Vaginal Cream. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System

Abnormal uterine bleeding/spotting, dysmenorrhea/pelvic pain, increase in size of uterine leiomyomata, vaginitis (including vaginal candidiasis), change in cervical secretion, cystitis-like syndrome, application site reactions of vulvovaginal discomfort, (including burning, irritation, and genital pruritus), endometrial hyperplasia, endometrial cancer, precocious puberty, leukorrhea.

Breasts

Tenderness, enlargement, pain, discharge, fibrocystic breast changes, breast cancer, gynecomastia in males.

Cardiovascular

Deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, increase in blood pressure.

Gastrointestinal

Nausea, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease.

Skin

Chloasma that may persist when drug is discontinued, loss of scalp hair, hirsutism, rash.

Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

Central Nervous System

Headache, migraine, dizziness, mental depression, nervousness, mood disturbances, irritability, dementia.

Miscellaneous

Increase or decrease in weight, glucose intolerance, edema, arthralgias, leg cramps, changes in libido, urticaria, anaphylactic reactions, exacerbation of asthma, increased triglycerides, hypersensitivity.

Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

DRUG INTERACTIONS

No formal drug interactions studies have been conducted in Premarin® Vaginal Cream.

Overview

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort (*Hypericum perforatum*) preparations, phenobarbital, phenytoin, carbamazepine, rifampicin, and dexamethasone may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

Lamotrigine:

Hormonal contraceptives containing estrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. The same interaction has been reported in women taking lamotrigine along with HRT containing estrogens.

Drug-Drug Interactions

No formal drug-drug interactions studies with Premarin® Vaginal Cream have been conducted (see Drug Interactions – Overview)

Drug-Food Interactions

No formal drug-food interactions studies with Premarin® Vaginal Cream have been conducted (see Drug Interactions – Overview)

CYP3A4 inhibitors such as grapefruit juice may increase plasma concentrations of 17 β -estradiol and may result in side effects.

Drug-Herb Interactions

It was found that some herbal products (e.g. St. John's wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be made 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 Test Interactions

There are no studies investigating drug-laboratory test interactions with Premarin® Vaginal Cream.

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

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity, increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;
- impaired glucose tolerance;
- increased plasma HDL and HDL₂ cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased serum triglycerides and phospholipids concentration.
- increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone (T₄), as measured by column or radioimmunoassay; T₃ resin uptake is decreased, reflecting the elevated TBG; free T₄ concentration is unaltered.

- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively, free or biologically active hormone concentrations are unchanged;
- The response to metyrapone may be reduced.
- The pathologist should be informed that the patient is receiving hormone replacement therapy (HRT) when relevant specimens are submitted.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks.

Drug-lifestyle interactions

Acute alcohol ingestion during HRT may lead to elevations in circulating estradiol levels.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Premarin[®] Vaginal Cream alone, or in combination with progestins therapy, should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinical appropriate to determine if treatment is still necessary (see boxed Warnings and Precautions). For women who have intact uteri, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding. In the absence of comparable data, the risks of HRT should be assumed to be similar for all estrogens and estrogen/progestin combinations.

Hormone replacement therapy (HRT) involving either estrogen alone or estrogen plus progestin combined therapy should only be continued as the benefits outweigh the risks for the individual.

Recommended Dose and Dosage Adjustment

Premarin[®] Vaginal Cream should be administered cyclically for short-term use only for the treatment of atrophic vaginitis, dyspareunia or kraurosis vulvae.

Premarin[®] Vaginal Cream should be instituted at the lowest effective dosage, and the need for continued estrogen therapy should be re-evaluated regularly.

For maintenance therapy one should always use the lowest dose that still proves effective. The requirement for hormone replacement therapy for menopausal symptoms should be reassessed periodically.

In some cases, hysterectomized women with a history of endometriosis may need a progestin, see **WARNINGS AND PRECAUTIONS, Endometriosis**.

Dosage Range

The lowest dose that will control symptoms should be chosen.

Low Dose

Premarin[®] Vaginal Cream (0.5g) is administered intravaginally or topically twice-weekly (for example, Monday and Thursday).

Maximum Recommended Dose

Premarin[®] Vaginal Cream is administered intravaginally or topically in a cyclic regimen (daily for 21 days and then off for 7 days). Generally, women should be started at the 0.5g daily dosage strength. Dosage adjustments (0.5 to 2 g) may be made based on individual response.

Appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

Instructions for Use of Applicator:

1. Remove cap.
2. Screw nozzle end of applicator onto the tube.
3. Gently squeeze tube to force sufficient cream into the barrel to provide the prescribed dose.
4. Unscrew applicator from tube.
5. Place the applicator into the vaginal opening.
6. To release medication, press plunger downward.

To Cleanse: Pull plunger out from barrel. Wash with mild soap and warm water.
DO NOT BOIL.

Missed Dose

If a patient misses a dose, it should be taken as soon as possible. If it is close to the patient's next scheduled dose, the missed dose should be skipped, and the patient should continue with her normal schedule. The patient should not take two doses at the same time.

Administration

Vaginal

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer.

OVERDOSAGE

Symptoms of overdose:

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects.

Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Treatment of overdose

There is no specific antidote and further treatment if necessary should be symptomatic.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Estrogens generally act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Estrogen receptors have been identified in various tissues including the wall of blood vessels, in tissues of the reproductive tract, breast, brain, liver and bone of women. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. Indirectly, they also contribute to the shaping of the skeleton, maintenance of tone and elasticity through the increase of collagen production in the supportive tissues of the heart, skin and urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Decline of ovarian estrogenic and progestogenic activity at the end of the menstrual cycle can result in menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the preovulatory or anovulatory cycle, estrogen is the primary determinant in the onset of menstruation.

Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which

secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate pituitary gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogen therapy acts to reduce elevated levels of these hormones seen in postmenopausal women.

Estrogen drug products act by regulating the transcription of a limited number of genes. They may act directly at the cell's surface via non "estrogen receptor" mechanism or directly with the estrogen receptor inside the cell. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects.

Estrogens used in therapy are also well absorbed through the skin and mucous membranes. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Pharmacodynamics

Currently, there are no pharmacodynamic data known for conjugated estrogens (CE) alone.

Conjugated estrogens used in therapy are soluble in water and are well absorbed through the skin, mucous membranes, and gastrointestinal tract after release from the drug formulation.

Effects on vasomotor symptoms associated with estrogen deficiency

Hot flushes, feelings of intense heat over the upper trunk and face, with flushing of the skin and sweating occur in approximately 80% of women as a result of the decrease in ovarian hormones. These vasomotor symptoms are seen in women whether menopause is surgically induced or spontaneous. However, hot flushes may be more severe in women who undergo surgical menopause. Hot flushes can begin before the cessation of menses.

Pharmacokinetics

Absorption

Conjugated estrogens are soluble in water and are well absorbed through the skin, mucous membranes, and the gastrointestinal tract after release from the drug formulation.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentration in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between esterified and non-esterified forms.

Estrogen drug products administered by non-oral routes, while not subject to true “first-pass” metabolism, do undergo significant hepatic uptake, metabolism, and enterohepatic recycling. Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted into the bile; however, they are re-absorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favour excretion through the kidneys since tubular re-absorption is minimal.

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency.

Excretion

A certain proportion of the estrogen is excreted into the bile, then reabsorbed from the intestine and returned to the liver through the portal venous system. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

Estradiol, estrone, and estriol are excreted in the urine, along with glucuronide and sulfate conjugates.

Special Populations and Conditions

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

STORAGE AND STABILITY

Store at 15°C - 30°C.

Keep out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

None required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PREMARIN[®] Vaginal Cream is available in tubes of 14 g and 30 g, each gram containing 0.625 mg of conjugated estrogens CSD. Each tube is accompanied with one (14g tube) or two (30g tube) calibrated plastic applicators.

Non-Medicinal Ingredients: Cetyl Alcohol, Cetyl Esters Wax, Glycerin, Glyceryl Monostearate, Methyl Stearate, Mineral Oil, Phenylethyl Alcohol, Propylene Glycol Monostearate, Sodium Lauryl Sulfate, Water Purified, White Wax.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Conjugated estrogens, C.S.D.

Chemical name: Not applicable

Molecular formula and molecular mass: Not applicable

Structural formula: Not applicable

Description: Conjugated estrogens C.S.D. contains a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of at least the following estrogens: estrone, equilin, 17α -dihydroequilin, 17α -estradiol, 17β -dihydroequilin, δ 8,9-dehydroestrone, 17β -estradiol, equilenin, 17α -dihydroequilenin, 17β -dihydroequilenin and as salts of their sulfate esters.

CLINICAL TRIALS

Effects on Vulvar and Vaginal Atrophy

A 12-week, prospective, randomized, double-blind placebo-controlled study was conducted to compare the safety and efficacy of 2 Premarin[®] Vaginal Cream (PVC) regimens 0.5 g (0.3 mg CE) administered twice weekly and 0.5 g (0.3 mg CE) administered sequentially for 21 days on drug followed by 7 days off drug to matching placebo regimens in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. The initial 12-week, double-blind, placebo-controlled phase was followed by an open-label phase to assess endometrial safety through week 52. The study randomized 423 generally healthy postmenopausal women between 44 to 77 years of age (mean 57.8 years), who at baseline had \leq 5 percent superficial cells on a vaginal smear, a vaginal pH \geq 5.0, and who identified a most bothersome moderate to severe symptom of vulvar and vaginal atrophy. The majority (92.2 percent) of the women were Caucasian (n = 390); 7.8 percent were Other (n = 33). All subjects were assessed for improvement in the mean change from baseline to Week 12 for the co-primary efficacy variables of: most bothersome symptom of vulvar and vaginal atrophy (defined as the moderate to severe symptom that had been identified by the woman as most bothersome to her at baseline); percentage of vaginal superficial cells and percentage of vaginal parabasal cells; and vaginal pH.

In the 12-week, double-blind phase, a statistically significant mean change between baseline and Week 12 in the symptom of dyspareunia was observed for both of the Premarin[®] Vaginal Cream regimens (0.5 g daily for 21 days, then 7 days off and 0.5 g twice weekly) compared to matching placebo. Also demonstrated for each Premarin[®] Vaginal Cream regimen compared to placebo was a statistically significant increase in the percentage of superficial cells at Week 12 (28 %, 21/7 regimen and 26 %, twice weekly, compared to 3 % and 1 % for matching placebo), a statistically significant decrease in parabasal cells (-61 %, 21/7 regimen and -58 %, twice weekly, compared to -21 % and -7 % for matching placebo) and statistically significant mean reduction between baseline and Week 12 in vaginal pH (-1.62, 21/7 regimen and -1.57, twice weekly, compared to -0.36 and -0.26 for matching placebo).

Endometrial safety was assessed by endometrial biopsy for all randomly assigned subjects at week 52. For the 155 subjects (83 on the 21/7 regimen, 72 on the twice-weekly regimen) completing the 52-week period with complete follow-up and evaluable endometrial biopsies, there were no reports of endometrial hyperplasia or endometrial carcinoma.

Published Studies

Vasomotor Symptoms and Vaginal Atrophy

The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) Study was an RCT to evaluate the safety and efficacy of lower doses of CEE and MPA in postmenopausal women. The design included a one year basic study to evaluate the efficacy of lower doses of CEE with and without MPA in relieving vasomotor symptoms (VMS) and vulvar and vaginal atrophy (VVA). A total of 2,673 healthy, postmenopausal women 40 to 65 years of age with an intact uterus (mean age of 53.3 years), including a vasomotor symptom efficacy-evaluable population (n=241 at baseline) participated.

Efficacy measures were frequency and severity of daily hot flushes and Papanicolaou smear with vaginal maturation index (VMI) to assess vaginal atrophy.

There were a total of eight treatment arms consisting of the following:

CEE 0.625 mg/day; CEE 0.625 mg/MPA 2.5 mg/day; CEE 0.45 mg/day; CEE 0.45 mg/MPA 2.5 mg/day; CEE 0.45 mg/MPA 1.5 mg/day; CEE 0.3 mg/day; CEE 0.3 mg/MPA 1.5 mg/day; or placebo.

Key observations for VMS: All active treatment groups significantly reduced mean number of hot flushes from baseline by week 1 or 2 ($P<0.01$) and all active treatment groups significantly reduced mean number of hot flushes compared with placebo by week 2 or 3 ($P<0.001$).

Numbers of hot flushes

- For the placebo group, the mean daily number of hot flushes dropped from approximately 10 at week 1, to approximately 5 at week 12, and continuing at approximately 5 to cycle 13.
- For the 0.625 mg CEE/2.5 mg MPA treatment group, the mean daily number of hot flushes decreased from approximately 10 at week 1, to approximately 1 at week 12, dropping to approximately 0.5 at cycle 13. The difference from placebo was significant ($P<0.5$) beginning from week 2 to the end of cycle 13.

Severity of hot flushes

A mild hot flush was rated a 1, a moderate hot flush a 2, and a severe hot flush a 3.

- For the placebo group, the mean daily severity of hot flushes decreased from approximately 2.1 at week 1, to approximately 1.7 at week 12, and continuing at approximately 1.7 to cycle 13.
- For the 0.625 mg CEE/2.5 mg MPA treatment group, the mean daily severity of hot flushes decreased from 2.1 at week 1, to approximately 0.5 at week 12, and dropping to approximately 0.2 at cycle 13. The difference from placebo was significant ($P<0.5$) beginning from week 2 to the end of cycle 13.

Key observations for VVA: All active treatment groups significantly increased the percentage of superficial cells from baseline at cycles 6 and 13 ($P<0.001$) and all active treatment groups significantly increased the percentage of superficial cells compared with placebo at cycles 6 and 13 ($P<0.001$).

DETAILED PHARMACOLOGY

See “Action and Clinical Pharmacology” section under the Health Professional Information Section.

TOXICOLOGY

Acute toxicity studies have been conducted with conjugated estrogens (Premarin®).

Acute Toxicity **Premarin®**

In studies conducted by Wyeth, Premarin (125 mg/kg) was administered orally. The LD₅₀ value for Premarin® administered orally or intraperitoneally to male and female CD-1 mice and CD rats was greater than 125 mg/kg.

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PART III: CONSUMER INFORMATION

Premarin® Vaginal Cream
(Conjugated Estrogens CSD 0.625 mg/g)

IMPORTANT: PLEASE READ

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

ABOUT THIS MEDICATION**What the medication is used for:**

- To treat vulvar and vaginal atrophy and kraurosis vulvae (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.
- To treat dyspareunia (pain during intercourse) associated with menopause.

Premarin® Vaginal Cream should not be used by women with intact uteri unless it is prescribed in association with a progestin.

Premarin® Vaginal Cream 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:

When using Premarin® Vaginal Cream women are using a hormone, estrogen (i.e. conjugated estrogens CSD 0.625 mg/g). Premarin® Vaginal Cream replaces estrogen specifically in and around the vagina which naturally decreases at menopause.

Estrogens are female hormones that are produced by a woman's ovaries and are necessary for normal sexual development and the regulation of menstrual periods during the childbearing years.

When a woman is between the ages of 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels and marks the beginning of menopause (the end of monthly menstrual periods). A sudden drop in estrogen levels also occurs if both ovaries are removed during an operation before natural menopause takes place. This is referred to as surgical menopause.

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes") as well as vaginal symptoms. In some women the symptoms are mild; in others they can be severe. These symptoms may last a few months or longer.

When it should not be used:

Before using Premarin® Vaginal Cream be sure to tell your doctor if you have any of the following medical problems, as Premarin® Vaginal Cream should not be used under these conditions:

- **Known, suspected, or past history of breast cancer.**
- **Known or suspected hormone-dependent cancer.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take Premarin® Vaginal Cream.
- **Unexpected or unusual vaginal bleeding**
- **Have (or have had) blood clot disorders, including blood clots in the legs or lungs or thrombophlebitis (inflammation of the veins).**
- **Serious liver disease**
- **Active or past history of heart disease, heart attacks or stroke.**
- **If you are allergic to Premarin® Vaginal Cream or any of its ingredients, or have had any unusual reactions to its ingredients (see **What the medicinal ingredients are and What the nonmedicinal ingredients are**).**
- **If you are pregnant or suspect you may be pregnant.** Since pregnancy may be possible early in pre-menopause while you are still having spontaneous periods, the use of non-hormonal birth control should be discussed with your physician at this time. If you accidentally take estrogen during pregnancy, there is a small risk of your unborn child having birth defects.
- If you have partially or completely lost vision due to blood vessel disease of the eye.
- If you have overgrowth of the lining of the uterus.
- Have known abnormality of the blood clotting system that increases your risk for having a blood clot (e.g. protein C, protein S, or antithrombin deficiency).
- If you experience migraines with or without aura.

What the medicinal ingredients are:

Conjugated equine estrogens

What the nonmedicinal ingredients are:

The cream contains the following inactive ingredients: Cetyl Alcohol, Cetyl Esters Wax, Glycerin, Glyceryl Monostearate, Methyl Stearate, Mineral Oil, Phenylethyl Alcohol, Propyl Glycol

Monostearate, Sodium Lauryl Sulfate, Water Purified, White Wax.

What dosage forms it comes in:

Premarin® Vaginal Cream is available in tubes of 14 g and 30g, each gram containing 0.625 mg of conjugated estrogens CSD. Each tube is accompanied with one (14g tube) or two (30g tube) calibrated plastic applicators.

Serious Warnings and Precautions

The Women’s Health Initiative (WHI) is a large clinical study that assessed the benefits and risks of oral combined *estrogen plus progestin* therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

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

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

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.
- 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.

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 HRT.

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-examination are recommended for all women. You should review technique for breast self-examination with your doctor.

Overgrowth of the lining of the uterus and cancer of the uterus

The use of *estrogen-alone* therapy by post-menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

If you still have your uterus, you should take a progestin medication (another hormone drug) regularly for a certain number of days of each month to reduce the risk of endometrial hyperplasia.

You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with you doctor. You should also report any unexpected or unusual vaginal bleeding to your doctor.

If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

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.

Heart Disease and Stroke

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

WARNINGS AND PRECAUTIONS

Breast Cancer

The results of the WHI trial indicated an increased risk of breast cancer in postmenopausal 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 post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Estrogens should not be taken by women who have a personal history of breast cancer.

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.

Gallbladder Disease

The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

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 post-menopausal 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 Premarin® Vaginal Cream talk to your doctor or pharmacist if you:

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)
- 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
- are pregnant or may be pregnant

- have had a hysterectomy (surgical removal of the uterus)
- smoke
- have been diagnosed with otosclerosis (hearing loss due to a problem with the bones in your ear)
- 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 been diagnosed with lupus.
- Premarin® Vaginal Cream may weaken and contribute to the failure of condoms, diaphragms, or cervical cap made of latex or rubber.

Other existing conditions you should discuss with your health professional include lupus, very low calcium levels, thyroid problems, fluid retention, gallbladder disease, depression, and breastfeeding. If you have upcoming surgery or prolonged bedrest, you should also discuss these.

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 (such as St. John's wort). Some medications (such as medications for high blood pressure, diabetes, blood clots, sleeping, anxiety, seizures, pain-relief and tuberculosis) may affect how Premarin® Vaginal Cream works. Premarin® Vaginal Cream may also affect how other medicines work.

You should also tell your doctor or pharmacist if you use latex or rubber diaphragms or cervical caps.

PROPER USE OF THIS MEDICATION

Usual Dose:

You should follow the dosage regimen prescribed by your healthcare provider.

Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example every 3 to 6 months) about the dose you are taking and whether you still need treatment with Premarin® Vaginal Cream.

Do not give Premarin® Vaginal Cream to other people, even if they have the same symptoms you have. It may harm them.

Instructions for Use of Applicator:

1. Remove cap.
2. Screw nozzle end of applicator onto the tube.
3. Gently squeeze tube to force sufficient cream into the barrel to provide the prescribed dose.
4. Unscrew applicator from tube.
5. Place the applicator into the vaginal opening.
6. To release medication, press plunger downward.

TO CLEANSE: Pull plunger out from barrel. Wash with mild soap and warm water. **DO NOT BOIL.**

Overdose:

Contact your physician or local Poison Control Center in case of accidental use of high doses of Premarin® Vaginal Cream.

Overdosage with estrogens may cause nausea and vomiting, breast discomfort, fluid retention, bloating or vaginal bleeding may occur in women. There is no specific antidote and further treatment if necessary should be symptomatic.

Overdosage may result in a period of amenorrhea (lack of menses) of a variable length and may be followed by irregular menses for several cycles. No cases of overdosage in male patients have been reported.

Missed Dose:

If you miss a dose, use it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not use 2 doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Breast pain, leaking of milk from the nipple
- Inflammation of the vagina, vaginal itching and/or discharge
- Breakthrough bleeding, spotting, changes in menstrual flow, painful periods
- Joint pain, leg pain
- Hair loss
- Changes in weight (increase or decrease)
- Nausea, vomiting, bloating, abdominal pain
- Dizziness
- Headache (including migraine)
- Changes in libido
- Mood disturbances, irritability
- Rash, itching, hives, tender red nodules on the shins and legs, acne

If any of these affects you severely, tell your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	Blood clot: Pain or swelling in the leg.			√
	Breast Cancer: Breast lump, unusual discharge.		√	
	Edema: Swelling of the hand and/or feet.	√		
	High Blood Pressure: headaches, dizziness, vision problems, shortness of breath		√	
	Persistent sad mood.			√
	Unexpected vaginal bleeding.		√	
Rare	Blood clot in the lung: Sharp pain in the chest, coughing blood or sudden shortness of breath.			√
	Stroke: Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg.			√
Very rare	Blood clot in the eye: Sudden partial or complete loss of vision.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Very rare	Liver disorder: Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.			√
Unknown	Angioedema and Severe Allergic Reactions: swelling of the face, eyes, or tongue, difficulty swallowing, wheezing, hives and generalized itching, rash, fever, abdominal cramps, chest discomfort or tightness, difficulty breathing, unconsciousness.			√
	Cerebrovascular insufficiency: visual disturbances, migraines, trouble speaking, paralysis or loss of consciousness.			√
	Gallbladder disorder: severe pain in the upper right abdomen, pain in the back between the shoulder blades, nausea and vomiting.		√	
Unknown	Heart Attack: Crushing chest pain or chest heaviness, pain in the arm, back, neck or jaw, shortness of breath, cold sweat, nausea, light-headedness.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	Heart palpitations	√		
	Increased blood sugar: frequent urination, thirst, and hunger.	√		
	Worsening of asthma: wheezing, coughing, shortness of breath, difficulty breathing			√

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

HOW TO STORE IT

Store Premarin® Vaginal Cream at 15° C to 30° C (room temperature).

Keep out of reach of children.

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/health-canada/services/drugs-health-products/medeffect-canada.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

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.pfizer.ca> or by contacting the sponsor, Pfizer Canada ULC, at: 1-800-463-6001

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