HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PREMARIN® VAGINAL CREAM safely and effectively. See full prescribing information for PREMARIN VAGINAL CREAM.

PREMARIN (conjugated estrogens) Vaginal Cream.
Initial U.S. Approval: 1946

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)**
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)**

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) (5.2)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)**

RECENT MAJOR CHANGES

Warnings and Precautions, Malignant Neoplasms (5.3)	02/2024

INDICATIONS AND USAGE

PREMARIN (conjugated estrogens) Vaginal Cream is a mixture of estrogens indicated for:

- Treatment of Atrophic Vaginitis and Kraurosis Vulvae (1.1)
- Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause (1.2)

DOSAGE AND ADMINISTRATION

- Cyclic administration of 0.5 to 2 g intravaginally [daily for 21 days then off for 7 days] for Treatment of Atrophic Vaginitis and Kraurosis Vulvae (2. 1)
- Cyclic administration of 0.5 g intravaginally [daily for 21 days then off for 7 days] for Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause (2. 2)
- Twice-weekly administration of 0.5 g intravaginally [for example, Monday and Thursday] for Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause (2. 2)

DOSAGE FORMS AND STRENGTHS

- Each gram contains 0.625 mg conjugated estrogens, USP (3)
- *Combination package:* Each contains a net wt. 1.06 oz (30 g) tube with plastic applicator(s) calibrated in 0.5 g increments to a maximum of 2 g (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.3)
- Known or suspected estrogen-dependent neoplasia (4, 5.3)
- Active DVT, PE, or a history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.2)
- Known anaphylactic reaction or angioedema to PREMARIN Vaginal Cream (5.16, 5.17)
- Known liver dysfunction or disease (4, 5.10)
- Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.5)

- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- Monitor thyroid function in women on thyroid replacement therapy (5.12, 5.21)

---------- **ADVERSE REACTIONS** ----------

In a prospective, randomized, placebo-controlled, double-blind study, the most common adverse reactions ≥ 2 percent are headache, pelvic pain, vasodilation, breast pain, leucorrhea, metrorrhagia, vaginitis, vulvovaginal disorder (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- **DRUG INTERACTIONS** ----------

Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

---------- **USE IN SPECIFIC POPULATIONS** ----------

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (5.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.3)]*.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)]*.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2)]*.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) -alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)]*.

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2)]*.

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.3), and Clinical Studies (14.2)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1 INDICATIONS AND USAGE

1.1 Treatment of Atrophic Vaginitis and Kraurosis Vulvae

1.2 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause

2 DOSAGE AND ADMINISTRATION

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.

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.3, 5.15)]*.

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2. 1Treatment of Atrophic Vaginitis and Kraurosis Vulvae

PREMARIN Vaginal Cream is administered intravaginally in a cyclic regimen (daily for 21 days and then off for 7 days). Generally, women should be started at the 0.5 g dosage strength. Dosage adjustments (0.5 to 2 g) may be made based on individual response *[see Dosage Forms and Strengths (3)]*.

2. 2Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause

PREMARIN Vaginal Cream (0.5 g) is administered intravaginally in a twice-weekly (for example, Monday and Thursday) continuous regimen or in a cyclic regimen of 21 days of therapy followed by 7 days off of therapy *[see Dosage Forms and Strengths (3)]*.

3 DOSAGE FORMS AND STRENGTHS

Each gram contains 0.625 mg conjugated estrogens, USP.

Combination package: Each contains a net wt. 1.06 oz (30 g) tube with plastic applicator(s) calibrated in 0.5 g increments to a maximum of 2 g.

4 CONTRAINDICATIONS

PREMARIN Vaginal Cream therapy should not be used in women with any of the following conditions:

- **Undiagnosed abnormal genital bleeding**
- **Known, suspected, or history of breast cancer**
- **Known or suspected estrogen-dependent neoplasia**
- **Active DVT, PE, or a history of these conditions**
- **Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions**
- **Known anaphylactic reaction or angioedema to PREMARIN Vaginal Cream**
- **Known liver dysfunction or disease**
- **Known protein C, protein S or antithrombin deficiency or other known thrombophilic disorders**
- **Known or suspected pregnancy**

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Systemic Absorption

Systemic absorption occurs with the use of PREMARIN Vaginal Cream. The warnings, precautions, and adverse reactions associated with oral PREMARIN treatment should be taken into account.

5.2 Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) -alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.2)]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) -alone versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.2)]*. The increase in risk was demonstrated after the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.2)]*.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.2)]*.

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg) -alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The

increase in VTE risk was demonstrated during the first 2 years[3] *[see Clinical Studies (14.2)]*. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted[4] *[see Clinical Studies (14.2)]*. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

5.3 Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. 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.

In a 52-week clinical trial using PREMARIN Vaginal Cream alone (0.5 g inserted twice weekly or daily for 21 days, then off for 7 days), there was no evidence of endometrial hyperplasia or endometrial carcinoma.

Breast Cancer

The WHI substudy of daily CE (0.625 mg)-alone provided information about breast cancer in estrogen-alone users. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80][5] [see *Clinical Studies (14.2)*].

After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[6] *[see Clinical Studies (14.2)]*.

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy and a smaller increased risk for estrogen-alone therapy, after several years of use. One large meta-analysis of prospective cohort studies reported increased risks that were dependent upon duration of use and could last up to > 10 years after discontinuation of estrogen plus progestin therapy and estrogen-alone therapy. Extension of the WHI trials also demonstrated increased breast cancer risk associated with estrogen plus progestin therapy.

Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms, requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77–3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7]

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27–1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

5.4 Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg) -alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83–2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8. 5), and Clinical Studies (14.3)]*.

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21–3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8. 5), and Clinical Studies (14.3)]*.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19–2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

5.5 Gallbladder Disease

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

5.6 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5.7 Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication 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, estrogens should be permanently discontinued.

5.8 Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

5.9 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.

5.10 Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5.11 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5.12 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens 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.

5.13 Fluid Retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogen-alone is prescribed.

5.14 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

5.15 Exacerbation of Endometriosis

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.

5.16 Anaphylactic Reaction and Angioedema

Cases of anaphylaxis, which develop within minutes to hours after taking orally-administered PREMARIN and require emergency management, have been reported in the postmarketing setting. Skin (hives, pruritus, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) involvement has been noted.

Angioedema involving the tongue, larynx, face, and feet requiring medical intervention has occurred postmarketing in patients taking orally-administered PREMARIN. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop an anaphylactic reaction with or without angioedema after treatment with oral PREMARIN should not receive oral PREMARIN again.

5.17 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

5.18 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

5.19 Effects on Barrier Contraception

PREMARIN Vaginal Cream exposure has been reported 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.

5.20 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy.

5.21 Drug-Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Malignant Neoplasms *[see Boxed Warning, Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a 12-week, randomized, double-blind, placebo-controlled trial of 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-2×/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, the most common adverse reactions ≥ 1 percent in the double blind phase are shown below (Table 1) *[see Clinical Studies (14.1)]*.

Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Reactions ≥ 1 Percent Only

	Treatment			
Body System*/Adverse Reaction	**PVC 21/7 N=143**	**Placebo 21/7 N=72**	**PVC 2×/week N=140**	**Placebo 2×/week N=68**
	Number (%) of Patients with Adverse Reaction			
Body As A Whole				
Abdominal Pain	1 (0.7)	1 (1.4)	0	1 (1.5)
Headache	5 (3.5)	1 (1.4)	3 (2.1)	1 (1.5)
Moniliasis	2 (1.4)	1 (1.4)	1 (0.7)	0
Pain	2 (1.4)	0	1 (0.7)	0
Pelvic Pain	4 (2.8)	2 (2.8)	4 (2.9)	0
Cardiovascular System				
Migraine	0	0	0	1 (1.5)
Vasodilation	3 (2.1)	2 (2.8)	2 (1.4)	0
Musculoskeletal System				
Muscle Cramp	2 (1.4)	0	0	0
Nervous System				

* Body system totals are not necessarily the sum of individual adverse events, since a patient may report two or more different adverse reactions in the same body system.

	Treatment			
Body System*/Adverse Reaction	**PVC 21/7 N=143**	**Placebo 21/7 N=72**	**PVC 2×/week N=140**	**Placebo 2×/week N=68**
	Number (%) of Patients with Adverse Reaction			
Dizziness	1 (0.7)	0	0	1 (1.5)
Skin and Appendages				
Acne	0	0	2 (1.4)	0
Erythema	0	1 (1.4)	0	0
Pruritus	2 (1.4)	1 (1.4)	1 (0.7)	0
Urogenital System				
Breast Enlargement	1 (0.7)	1 (1.4)	0	0
Breast Pain	7 (4.9)	0	3 (2.1)	0
Dysuria	2 (1.4)	0	0	0
Leukorrhea	3 (2.1)	1 (1.4)	4 (2.9)	5 (7.4)
Metrorrhagia	0	0	0	2 (2.9)
Urinary Frequency	0	1 (1.4)	0	0
Urinary Tract Infection	0	1 (1.4)	0	0
Urinary Urgency	1 (0.7)	1 (1.4)	0	0
Vaginal Hemorrhage	2 (1.4)	0	1 (0.7)	1 (1.5)
Vaginal Moniliasis	2 (1.4)	0	0	0
Vaginitis	2 (1.4)	1 (1.4)	3 (2.1)	3 (4.4)
Vulvovaginal Disorder	4 (2.8)	0	3 (2.1)	2 (2.9)

* Body system totals are not necessarily the sum of individual adverse events, since a patient may report two or more different adverse reactions in the same body system.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of 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 or spotting, dysmenorrhea or 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, exacerbation of asthma, increased triglycerides, hypersensitivity.

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

7 DRUG INTERACTIONS

No drug interaction studies have been conducted for PREMARIN Vaginal Cream.

7.1 Metabolic Interactions

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, carbamazepine, and rifampin, 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 erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

PREMARIN Vaginal Cream should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8.3 Nursing Mothers

PREMARIN Vaginal Cream should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogen therapy. Caution should be exercised when PREMARIN Vaginal Cream is administered to a nursing woman.

8.4 Pediatric Use

PREMARIN Vaginal Cream is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

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.

The Women's Health Initiative Studies

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Warnings and Precautions (5.2), and Clinical Studies (14.2)]*.

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Warnings and Precautions (5.2, 5.3), and Clinical Studies (14.2)]*.

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions (5.4), and Clinical Studies (14.3)]*.

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Warnings and Precautions (5.4), and Clinical Studies (14.3)]*.

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of PREMARIN Vaginal Cream has not been studied.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of PREMARIN Vaginal Cream has not been studied.

10 OVERDOSAGE

Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of PREMARIN therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

Each gram of PREMARIN (conjugated estrogens) Vaginal Cream contains 0.625 mg conjugated estrogens, USP in a nonliquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. PREMARIN Vaginal Cream is applied intravaginally.

PREMARIN Vaginal Cream contains a mixture of conjugated 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 sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. 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 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, which is secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens 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.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

12.2 Pharmacodynamics

Currently, there are no pharmacodynamic data known for PREMARIN Vaginal Cream.

12.3 Pharmacokinetics

Absorption

Conjugated estrogens are water soluble and are well-absorbed through the skin, mucous membranes, and the gastrointestinal (GI) tract. The vaginal delivery of estrogens circumvents first-pass metabolism.

A bioavailability study was conducted in 24 postmenopausal women with atrophic vaginitis. The mean (SD) pharmacokinetic parameters for unconjugated estrone, unconjugated estradiol, total estrone, total estradiol and total equilin following 7 once-daily doses of PREMARIN Vaginal Cream 0.5 g is shown in Table 2.

Table 2: Mean ± SD Pharmacokinetic Parameters of PREMARIN Following Daily Administration (7 Days) of PREMARIN Vaginal Cream 0.5 g in 24 Postmenopausal Women

Pharmacokinetic Profiles of Unconjugated Estrogens PREMARIN Vaginal Cream 0.5 g			
PK Parameters Arithmetic Mean ± SD	**C_{max} (pg/mL)**	**T_{max} (hr)**	**AUC_{ss} (pg•hr/mL)**
Estrone	42.0 ± 13.9	7.4 ± 6.2	826 ± 295
Baseline-adjusted estrone	21.9 ± 13.1	7.4 ± 6.2	365 ± 255
Estradiol	12.8 ± 16.6	8.5 ± 6.2	231 ± 285
Baseline-adjusted estradiol	9.14 ± 14.7	8.5 ± 6.2	161 ± 252
Pharmacokinetic Profiles of Conjugated Estrogens PREMARIN Vaginal Cream 0.5 g			
PK Parameters Arithmetic Mean ± SD	**C_{max} (ng/mL)**	**T_{max} (hr)**	**AUC_{ss} (ng•hr/mL)**
Total estrone	0.60 ± 0.32	6.0 ± 4.0	9.75 ± 4.99
Baseline-adjusted total estrone	0.40 ± 0.28	6.0 ± 4.0	5.79 ± 3.7
Total estradiol	0.04 ± 0.04	7.7 ± 5.9	0.70 ± 0.42
Baseline-adjusted total estradiol	0.04 ± 0.04	7.7 ± 6.0	0.49 ± 0.38
Total equilin	0.12 ± 0.15	6.1 ± 4.7	3.09 ± 1.37

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 SHBG and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

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

Use in Specific Populations

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

14 CLINICAL STUDIES

14.1 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 ≤ 5 percent superficial cells on a vaginal smear, a vaginal pH ≥ 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, see Table 3. 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 percent, 21/7 regimen and 26 percent, twice a week compared to 3 percent and 1 percent for matching placebo), a statistically significant decrease in parabasal cells (-61 percent, 21/7 regimen and -58 percent, twice a week compared to -21 percent and -7 percent 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 a week 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.

Table 3: Mean Change in Dyspareunia Severity Compared to Placebo MITT Population of Most Bothersome Symptom Score for Dyspareunia, LOCF

Dyspareunia	**PVC 0.5 g 21/7***	**Placebo 0.5 g 21/7***	**PVC 0.5 g 2×/wk†**	**Placebo 0.5 g 2×/wk†**
Baseline	n Mean (SD) 50 **2.26 (0.99)**	n Mean (SD) 18 **2.32 (0.88)**	n Mean (SD) 52 **2.43 (0.76)**	n Mean (SD) 22 **2.28 (1.04)**
Week 12	50 **0.77 (1.05)**	18 **1.93 (1.03)**	52 **0.88 (0.96)**	21 **1.63 (1.16)**
Change from Baseline at Week 12	50 **-1.48 (1.17)**	18 **-0.40 (1.01)**	52 **-1.55 (0.92)**	21 **-0.62 (1.23)**
P-value vs. Placebo	<0.001 ‡	--	<0.001 §	--

* PVC 21/7 = apply PVC for 21 days and then 7 days of no therapy

† PVC 2×/wk = apply PVC twice a week

‡ Comparison of PVC 21/7 with placebo 21/7

§ Comparison of PVC 2×/wk with placebo 2×/wk

14.2 Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. These substudies did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen--alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in Table 4.

Table 4: Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI*

Event	**Relative Risk CE vs. Placebo (95% nCI†)**	**CE n = 5,310**	**Placebo n = 5,429**
		Absolute Risk per 10,000 Women-Years	
CHD events‡	0.95 (0.78–1.16)	54	57
Non-fatal MI‡	*0.91 (0.73–1.14)*	*40*	*43*
CHD death‡	*1.01 (0.71–1.43)*	*16*	*16*
All Strokes‡	1.33 (1.05–1.68)	45	33
Ischemic stroke‡	*1.55 (1.19–2.01)*	*38*	*25*
Deep vein thrombosis‡,§	1.47 (1.06–2.06)	23	15
Pulmonary embolism‡	1.37 (0.90–2.07)	14	10
Invasive breast cancer‡	0.80 (0.62–1.04)	28	34
Colorectal cancer¶	1.08 (0.75–1.55)	17	16
Hip fracture‡	0.65 (0.45–0.94)	12	19
Vertebral fractures‡,§	0.64 (0.44–0.93)	11	18
Lower arm/wrist fractures‡,§	0.58 (0.47–0.72)	35	59

* Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

† Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

‡ Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

§ Not included in "global index."

¶ Results are based on an average follow-up of 6.8 years.

All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

Þ A subset of the events was combined in a “global index” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Event	Relative Risk CE vs. Placebo (95% nCI[†])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
Total fractures[‡,§]	0.71 (0.64–0.80)	144	197
Death due to other causes[¶,#]	1.08 (0.88–1.32)	53	50
Overall mortality[‡,§]	1.04 (0.88–1.22)	79	75
Global Index[Þ]	1.02 (0.92–1.13)	206	201

[*] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

[†] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[‡] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

[§] Not included in "global index."

[¶] Results are based on an average follow-up of 6.8 years.

[#] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

[Þ] A subset of the events was combined in a “global index” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.[9] The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined.[10]

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy, stratified by age, showed in women 50 to 59 years of age a non-significant trend toward reduced risk for CHD *[hazard ratio (HR) 0.63 (95 percent CI, 0.36–1.09)]* and overall mortality *[HR 0.71 (95 percent CI, 0.46–1.11)]*.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 5. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 5: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[*,†]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[‡])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99–1.53)	41	34
Non-fatal MI	*1.28 (1.00–1.63)*	*31*	*25*
CHD death	*1.10 (0.70–1.75)*	*8*	*8*
All Strokes	1.31 (1.03–1.68)	33	25
Ischemic stroke	*1.44 (1.09–1.90)*	*26*	*18*
Deep vein thrombosis[§]	1.95 (1.43–2.67)	26	13
Pulmonary embolism	2.13 (1.45–3.11)	18	8
Invasive breast cancer[¶]	1.24 (1.01–1.54)	41	33
Colorectal cancer	0.61 (0.42–0.87)	10	16
Endometrial cancer[§]	0.81 (0.48–1.36)	6	7
Cervical cancer[§]	1.44 (0.47–4.42)	2	1
Hip fracture	0.67 (0.47–0.96)	11	16
Vertebral fractures[§]	0.65 (0.46–0.92)	11	17

[*] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

[†] Results are based on centrally adjudicated data.

[‡] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[§] Not included in "global index."

[¶] Includes metastatic and non-metastatic breast cancer, with the exception of *in situ* cancer.

[#] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

[Þ] A subset of the events was combined in a "global index" defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Event	Relative Risk CE/MPA vs. Placebo (95% nCI‡)	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
Lower arm/wrist fractures§	0.71 (0.59–0.85)	44	62
Total fractures§	0.76 (0.69–0.83)	152	199
Overall Mortality#	1.00 (0.83–1.19)	52	52
Global IndexÞ	1.13 (1.02–1.25)	184	165

* Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

† Results are based on centrally adjudicated data.

‡ Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

§ Not included in "global index."

¶ Includes metastatic and non-metastatic breast cancer, with the exception of *in situ* cancer.

All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

Þ A subset of the events was combined in a "global index" defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age, a non-significant trend toward reduced risk for overall mortality *[HR 0.69 (95 percent CI, 0.44–1.07)]*.

14.3 Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) -alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83–2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)]*.

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years; 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21–3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)]*.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19–2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)]*.

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10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation*. 2006;113:2425–2434.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PREMARIN (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

Combination package: Each contains a net wt. of 1.06 oz (30 g) tube with plastic applicator(s) calibrated in 0.5 g increments to a maximum of 2 g (NDC 0046-0872-21).

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information and Instructions for Use).

17.1 Vaginal Bleeding

Inform postmenopausal women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.3)]*.

17.2 Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions (5.2, 5.3, 5.4)]*.

17.3 Possible Less Serious but Common Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.

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FDA-Approved Patient Labeling

PREMARIN® (prem-uh-rin)
(Conjugated estrogens) Vaginal Cream

Read this PATIENT INFORMATION before you start using PREMARIN Vaginal Cream and read what you get each time you refill your PREMARIN Vaginal Cream prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about PREMARIN Vaginal Cream (an estrogen mixture)?

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb) Report any unusual vaginal bleeding right away while you are using PREMARIN Vaginal Cream. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline in brain function)
- Using estrogen-alone may increase your chances of getting strokes or blood clots
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women age 65 years of age or older
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women age 65 years of age or older
- You and your healthcare provider should talk regularly about whether you still need treatment with PREMARIN Vaginal Cream

What is PREMARIN Vaginal Cream?

PREMARIN Vaginal Cream is a medicine that contains a mixture of estrogen hormones.

What is PREMARIN Vaginal Cream used for?

PREMARIN Vaginal Cream is used after menopause to:

- **Treat menopausal changes in and around the vagina**
  You and your healthcare provider should talk regularly about whether you still need treatment with PREMARIN Vaginal Cream to control these problems.
- **Treat painful intercourse caused by menopausal changes of the vagina**

Who should not use PREMARIN Vaginal Cream?

Do not start using PREMARIN Vaginal Cream if you:

- **Have unusual vaginal bleeding**
- **Currently have or have had certain cancers**
  Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use PREMARIN Vaginal Cream.
- **Had a stroke or heart attack**
- **Currently have or have had blood clots**
- **Currently have or have had liver problems**
- **Have been diagnosed with a bleeding disorder**
- **Are allergic to PREMARIN Vaginal Cream or any of its ingredients**
  See the list of ingredients in PREMARIN Vaginal Cream at the end of this leaflet.
- **Think you may be pregnant**

Tell your healthcare provider:

- **If you have unusual vaginal bleeding**
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **About all of your medical problems**
  Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **About all the medicines you take**
  This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PREMARIN Vaginal Cream works. PREMARIN Vaginal Cream may also affect how your other medicines work.
- **If you are going to have surgery or will be on bedrest**
  You may need to stop using PREMARIN Vaginal Cream.
- **If you are breast feeding**
  The estrogen hormones in PREMARIN Vaginal Cream can pass into your breast milk.

How should I use PREMARIN Vaginal Cream?

PREMARIN Vaginal Cream is a cream that you place in your vagina with the applicator provided with the cream.

- Take the dose recommended by your healthcare provider and talk to him or her about how well that dose is working for you
- 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
- Step 1. Remove cap from tube.
- Step 2. Screw nozzle end of applicator onto tube (Figure A).

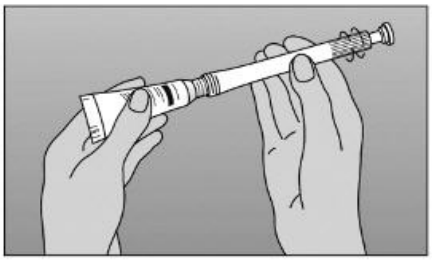

Figure A

- Step 3. *Gently* squeeze tube from the *bottom* to force sufficient cream into the barrel to provide the prescribed dose. Use the marked stopping points on the applicator to measure the correct dose, as prescribed by your healthcare provider (Figure B).

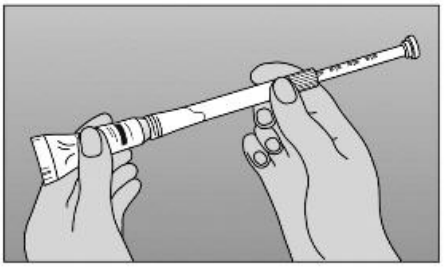

Figure B

- Step 4. Unscrew applicator from tube.
- Step 5. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position (Figure C).

Figure C

Step 6. TO CLEANSE: Pull plunger to remove it from barrel. Wash with mild soap and warm water (Figure D).

DO NOT BOIL OR USE HOT WATER.

Figure D

What are the possible side effects of PREMARIN Vaginal Cream?

PREMARIN Vaginal Cream is only used in and around the vagina; however, the risks associated with oral estrogens should be taken into account.

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- Heart attack
- Stroke
- Blood clots
- Dementia
- Breast cancer
- Cancer of the lining of the uterus (womb)
- Cancer of the ovary
- High blood pressure
- High blood sugar
- Gallbladder disease
- Liver problems
- Enlargement of benign tumors of the uterus ("fibroids")
- Severe allergic reaction

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- New breast lumps
- Unusual vaginal bleeding
- Changes in vision or speech
- Sudden new severe headaches
- Severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- Swollen lips, tongue or face
- **Less serious, but common side effects include:**
- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach or abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection
- Reactions from inserting PREMARIN Vaginal Cream, such as vaginal burning, irritation, and itching

These are not all the possible side effects of PREMARIN Vaginal Cream. For more information, ask your healthcare provider or pharmacist for advice about side effects. You may report side effects to Pfizer Inc. at 1-800-438-1985 or to FDA at 1-800-FDA-1088.

What can I do to lower my chances of getting a serious side effect with PREMARIN Vaginal Cream?

- Talk with your healthcare provider regularly about whether you should continue using PREMARIN Vaginal Cream
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you
  The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus. See your healthcare provider right away if you get vaginal bleeding while using PREMARIN Vaginal Cream.
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else
  If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease
  Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about the safe and effective use of PREMARIN Vaginal Cream

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use PREMARIN Vaginal Cream for conditions for which it was not prescribed. Do not give PREMARIN Vaginal Cream to other people, even if they have the same symptoms you have. It may harm them.

Keep PREMARIN Vaginal Cream out of the reach of children.

Latex or rubber condoms, diaphragms and cervical caps may be weakened and fail when they come into contact with PREMARIN Vaginal Cream.

This leaflet provides a summary of the most important information about PREMARIN Vaginal Cream. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about PREMARIN Vaginal Cream that is written for health professionals.

What are the ingredients in PREMARIN Vaginal Cream?

PREMARIN Vaginal Cream contains a mixture of conjugated estrogens, which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components, including sodium sulfate conjugates: 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin. PREMARIN Vaginal Cream also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.

PREMARIN (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

Combination package: Each contains a net wt. of 1.06 oz (30 g) tube with plastic applicator(s) calibrated in 0.5 g increments to a maximum of 2 g (NDC 0046-0872-21).

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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