TREATING AT THE SOURCE

Treating at the source with Premarin® (conjugated estrogens) Vaginal Cream 0.5 g twice weekly.

Restores estrogen, which helps rebuild vaginal tissue while on treatment.¹

**Significant improvement in VMI was seen at week 12 vs baseline (n=139)²**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>After 12 weeks of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8% superficial cells increased to 26.1%*</td>
<td>1.9%* (0.5 g 2x/wk (group))</td>
</tr>
<tr>
<td>Intermediate cells</td>
<td>Intermediate cells</td>
</tr>
<tr>
<td>Basal cells</td>
<td>Basal cells</td>
</tr>
<tr>
<td>59.5% parabasal cells decreased</td>
<td></td>
</tr>
</tbody>
</table>

This image is for illustrative purposes only; individual results may vary. *P < .001 vs baseline.

IMPORTANT SAFETY INFORMATION

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.

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) estrogen alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women with daily oral conjugated estrogens (CE) alone. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke, and myocardial infarction in postmenopausal women with daily oral CE combined with medroxyprogesterone acetate (MPA). In the absence of comparable data, these risks should be assumed to be similar for other dosage forms of estrogens.

The WHI Memory Study (WHIMS) reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older, in both the estrogen alone and estrogen plus progestin arms. It is unknown whether these findings apply to younger postmenopausal women.

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer.

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

Please see accompanying Full Prescribing Information, including BOXED WARNING.

Please see Important Safety Information and Indications continued on the next page.
IMPORTANT SAFETY INFORMATION (CONTINUED)

PREMARIN VAGINAL CREAM should not be used in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or a history of breast cancer; known or suspected estrogen-dependent neoplasia; active deep vein thrombosis, pulmonary embolism, or a history of these conditions; active arterial thromboembolic disease (e.g., stroke, myocardial infarction), or a history of these conditions; anaphylactic reaction or angioedema to Premarin Vaginal Cream; liver dysfunction or disease; thrombophilic disorders; pregnancy.

Estrogens increase the risk of gallbladder disease. Discontinue estrogen if loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs. Monitor thyroid function in women on thyroid replacement therapy, because estrogens may be associated with increased thyroid binding globulin (TBG) levels.

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

INDICATIONS

Premarin Vaginal Cream is indicated for the treatment of atrophic vaginitis and kraurosis vulvae; and for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

For more information, visit www.pvchcp.com.

STUDY DESCRIPTION

Bachmann Study Description: Results from a 12-week, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of Premarin Vaginal Cream 0.5 g for the treatment of vulvovaginal atrophy in generally healthy postmenopausal women aged 44 to 77 years (N=423). Premarin Vaginal Cream was administered using 2 dosing regimens: twice weekly and once daily (21 days on/7 days off). The study consisted of an initial 12-week trial followed by an open-label extension to assess endometrial safety through Week 52 (n=155). Primary endpoints were the changes from baseline in Vaginal Maturation Index, vaginal pH, and severity of patient-reported most bothersome symptom (vaginal dryness, itching, burning, or dyspareunia) at Week 12. Participants defined the severity of their most bothersome symptom on the following scale: 1=mild, 2=moderate, 3=severe; and at least 1 symptom had to be moderate to severe. For most women, dyspareunia was identified as the most bothersome symptom at baseline. Weekly severity score is an average of the daily scores.¹,²

REFERENCES


Please see accompanying Full Prescribing Information, including BOXED WARNING.
PREMARIN® (conjugated estrogens)
Vaginal Cream

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.

1 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)

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

See full prescribing information for complete boxed warning.

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

2 DOSAGE AND ADMINISTRATION
2.1 Treatment of Atrophic Vaginitis and Kraurosis Vulvae
2.2 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause

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4 CONTRAINDICATIONS

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5.2 Cardiovascular Disorders
5.3 Malignant Neoplasms
5.4 Probable Dementia
5.5 Gallbladder Disease
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5.7 Visual Abnormalities
5.8 Addition of a Progestin When a Woman Has Not Had a Hysterectomy
5.9 Effects on Barrier Contraception
5.10 Hypertiglyceridemia
5.11 Hepatic Impairment and/or Past History of Cholestatic Jaundice
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5.13 Fluid Retention
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FDA-Approved Patient Labeling

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

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)
• 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)

DOSE 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, or a net wt. 1.5 oz (42.5 g) tube with one plastic applicator 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 galbladder disease (5.5)
• Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertiglyceridemia 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: 05/2012
**INDICATIONS AND USAGE**

PREMARIN Vaginal Cream is administered intravaginally in a cyclic regimen (daily for 21 days of therapy followed by 7 days off of therapy [see Dosage Forms and Strengths (3)]. 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)].

**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

**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, obesity and syndrome X [VTE] for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

5.3 Malignant Neoplasms

Endometrial Cancer

- 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 4 [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).

BREAST CANCER and PROBABLE DEMENTIA

- 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 (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.

Cardiovascular Disorders and Probable Dementia

- 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 (33 versus 25 per 10,000 women-years) [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 statistically significant increased risk of stroke was reported in women 50 to 59 years of age receiving daily CE (0.625 mg)-alone compared to placebo 2 [see Clinical Studies (14.2)]. Should a VTE occur or be suspected, estrogen-alone 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).

- 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 in the same age group receiving placebo (33 versus 25 per 10,000 women-years) [see Clinical Studies (14.2)]. Should any of these occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

- 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 of therapy. 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 persisted1 [see Clinical Studies (14.2)]. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

- In the WHI estrogen-alone substudy, a statistically 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.

5.4 Women 65 Years of Age or Older

- The WHI estrogen-alone substudy 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 oral conjugated estrogens (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) and 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 dose and for the shortest duration consistent with treatment goals and risks for the individual woman.

5.5 Women 50 to 54 Years of Age

- The WHI estrogen plus progestin substudy reported an increased risk of developing probable dementia in postmenopausal women 50 to 59 years of age during 5.6 years of treatment with daily oral CE (0.625 mg) plus MPA [2.5 mg]-alone, 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) plus 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 dose 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

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

1.2 DOSAGE AND ADMINISTRATION

- Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be added 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, 3.15)].

- Use 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. **TREATMENT 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 to 0.25 or 0.5 g may be made based on individual response [see Dosage Forms and Strengths (3)].

2.1 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vaginal 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, or a net wt. 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5 g increments to a maximum of 2 g.
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/7 days), there was no evidence of endometrial hyperplasia or endometrial carcinoma.

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg) alone. 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] [see Clinical Studies (14.2)].

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 7.1 years, daily CE plus MPA was associated with 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 1.09, and the absolute risk was 40 versus 36 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 0.86, and the absolute risk was 45 versus 55 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 younger age than the invasive breast cancers in the CE-alone 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 were similar between the two groups [see Clinical Studies (14.2)].

Consistent with the WHI clinical trial, 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. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the effect of estrogen alone or estrogen plus progestin therapy is not as strong as 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 estrogen-alone users across different populations, ethnicities, 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 7.1 years, the relative risk for cancer as compared to 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. In some epidemiologic studies of estrogen plus progestin products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

5.4 Probable Dementia

In the WHI estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized 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 7.1 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 plus MPA, and the absolute risk was 45 versus 55 cases per 100,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.3)].

In the WHI 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, and the absolute risk was 45 versus 36 cases per 100,000 women-years [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 estrogen-alone and estrogen plus progestin studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [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 estrogen 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 and refer the patient to an ophthalmologist.

IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; these findings apply to younger postmenopausal women [see Use in Specific Populations (8.5), and Clinical Studies (14.3)].

5.12 Hypothyroidism

Increased thyroid-stimulating hormone (TSH) levels have been reported in some postmenopausal women taking estrogen. 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.

5.14 Hypocalcemia

Estrogens should be used in caution with women having parathyroid hyperplasia 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/or respiratory tract (respiratory constriction or airway obstruction) involvement have been reported in patients taking orally-administered PREMARIN. Angioedema involving 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.

6.0 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.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates in the clinical trials of another drug 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. Data were included in the PVC-217 treatment group (0.5 g PVC daily for 21 days, then 7 days off), 27 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, the most common adverse reactions 2 percent in the double blind phase are shown below (Table 1) [see Clinical Studies (14.1)].
PREMARIN Vaginal Cream should not be used during pregnancy [see Contraindications (4)]. There may be 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 [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.

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

9. 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, and other ingredients. 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-dihydroequiin.

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, i.e., 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>
<thead>
<tr>
<th>Body System</th>
<th>PVC</th>
<th>Placebo</th>
<th>PVC</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>1 (0.7)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (3.5)</td>
<td>1 (1.4)</td>
<td>3 (2.1)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Migraine</td>
<td>2 (1.4)</td>
<td>1 (1.4)</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pelvic Pain</td>
<td>4 (2.8)</td>
<td>2 (2.8)</td>
<td>4 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Migraine</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>3 (2.1)</td>
<td>2 (2.8)</td>
<td>2 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Dizziness</td>
<td>1 (0.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>Acne</td>
<td>0</td>
<td>0</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Erythema</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (1.4)</td>
<td>1 (1.4)</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Urogenital System</td>
<td>Breast Enlargement</td>
<td>1 (0.7)</td>
<td>1 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Breast Pain</td>
<td>7 (4.9)</td>
<td>0</td>
<td>3 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Dysuria</td>
<td>2 (1.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leukorrhea</td>
<td>3 (2.1)</td>
<td>1 (1.4)</td>
<td>4 (2.8)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Urinary Frequency</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Urgency</td>
<td>1 (0.7)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vaginal Hemorrhage</td>
<td>2 (1.4)</td>
<td>0</td>
<td>1 (0.7)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Vaginal Moniliasis</td>
<td>2 (1.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>2 (1.4)</td>
<td>1 (1.4)</td>
<td>3 (2.1)</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>Vulvovaginal Disorder</td>
<td>4 (2.8)</td>
<td>0</td>
<td>3 (2.1)</td>
<td>2 (2.9)</td>
</tr>
</tbody>
</table>

* 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 generalized pruritus, endometrial hyperplasia, endometrial cancer, precocious pubertery, leukorrhoea.

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

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

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

Skin
Itchiness 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 isozyme CYP3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect drug metabolic pathways. 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 changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythrocytin, diltiazem, ketoconazole, itraconazole, rifabutin 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.
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 free days off 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 and parabasal cells and percentage of vaginal parabasal cells; and vaginal pH.

Endometrial safety was assessed by endometrial biopsy for all randomly assigned subjects at week 52. Subjects who completed the study entered an open-label extension phase 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 across baseline and Week 12 in the symptom of dyspareunia was observed for both of the PREMARIN Vaginal Cream regimens (0.5 g twice weekly and 0.5 g (0.3 mg CE) administered sequentially for 21 days on drug free days off 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 and 26 percent, respectively) compared to 3 percent and 1 percent for matching placebo, a statistically significant decrease in parabasal cells (-61 percent and -58 percent, respectively, compared to -21 percent and -7 percent for matching placebo) and statistically significant mean reductions in the symptom of dyspareunia and Week 12 in vaginal pH (-1.82 and -1.57, respectively, 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 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 (fatal and non-fatal), 26 more deep vein thromboses, and 5 fewer hip fractures.5 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.

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 (fatal and non-fatal), 26 more deep vein thromboses, and 5 fewer hip fractures.5 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.

Central 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 intracerebral hemorrhages in women receiving CE-alone compared to placebo. Estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

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 CE (0.625 mg) and CE plus 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.

Table 3: Mean Change in Dyspareunia Severity Compared to Placebo MITT Population of MostBothersome Symptom Score for Dyspareunia, LOCFA

<table>
<thead>
<tr>
<th>Dyspareunia</th>
<th>PVC 0.5 g</th>
<th>Placebo</th>
<th>PVC 0.5 g</th>
<th>Placebo</th>
<th>PVC 0.5 g</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Week 12</td>
<td>2.43 (0.76)</td>
<td>2.28 (1.04)</td>
<td>2.26 (0.99)</td>
<td>2.32 (0.88)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change from Baseline to Week 12

<table>
<thead>
<tr>
<th>Week 52</th>
<th>0.88 (0.96)</th>
<th>2.11 (1.16)</th>
<th>0.77 (1.05)</th>
<th>1.93 (1.03)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from Baseline</td>
<td>-1.55 (0.92)</td>
<td>-0.62 (1.23)</td>
<td>-1.48 (1.17)</td>
<td>-0.40 (1.01)</td>
</tr>
</tbody>
</table>

P-value vs. Placebo

| P-value vs. Placebo | <0.001f | <0.001f |

14.2.3 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 CE (0.625 mg) and CE plus 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.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th>CE/MPA vs. Placebo (95% CI)</th>
<th>CE/MPA n = 8,506</th>
<th>Placebo n = 8,102</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>1.23 (0.99–1.53)</td>
<td>41</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.28 (1.00–1.63)</td>
<td>31</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>CHD death</td>
<td>1.10 (0.70–1.75)</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>All strokes</td>
<td>1.33 (1.03–1.71)</td>
<td>30</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.44 (1.09–1.92)</td>
<td>20</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.95 (1.43–2.67)</td>
<td>26</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.13 (1.45–3.11)</td>
<td>18</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
Table 5: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years<sup>10</sup> (Cont.)

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE/MPA vs. Placebo (95% nCI&lt;sup&gt;4&lt;/sup&gt;)</th>
<th>CE/MPA n = 8,506</th>
<th>Placebo n = 8,102</th>
<th>Absolute Risk per 10,000 Women-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive breast cancer&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1.24 (1.01-1.54)</td>
<td>41</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.61 (0.42-0.87)</td>
<td>10</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Endometrial cancer&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.87 (0.48-1.36)</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1.44 (0.47-4.42)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.67 (0.47-0.96)</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Verterbral fractures&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.65 (0.46-0.92)</td>
<td>11</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Lower arm/wrist fractures&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.71 (0.59-0.85)</td>
<td>44</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Total fractures&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.76 (0.69-0.83)</td>
<td>152</td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>1.00 (0.83-1.19)</td>
<td>52</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Global Index&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1.13 (1.02-1.25)</td>
<td>184</td>
<td>165</td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from numerous WHI publications. WHI publications can be viewed at www.nihbi.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.
* 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 2,247 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 or 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 75 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 (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 or 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)].

15 REFERENCES


16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied

PREMARIN (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.
FDA-Approved Patient Labeling
PREMARIN® (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

- 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 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).
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).
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).
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.

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: 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin. PREMARIN Vaginal Cream also contains cetyl esters wax, cetyl alcohol, white wax, glycerol 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), or a net wt. 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5 g increments to a maximum of 2 g (NDC 0046-0872-93).

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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