IMPORTANT SAFETY INFORMATION AND INDICATIONS (continued on next page)

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.

Please see accompanying Full Prescribing Information, including BOXED WARNING.
IMPORTANT SAFETY INFORMATION (continued)

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.

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.premarinvaginalcreamhcp.com.

STUDY DESCRIPTION

Bachmann: 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.1-3

Please see accompanying Full Prescribing Information, including BOXED WARNING.

PREMARIN (conjugated estrogens) Vaginal Cream.

Initial U.S. Approval: 1946

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**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)

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**INDICATIONS AND USAGE**

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

- Treatment of Atrophic Vaginitis and Kraurosis Vulvae
- Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause
- Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause (2.2)

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**WARNINGS AND PRECAUTIONS**

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

**ADVERSE REACTIONS**

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 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 (4.2, 4.5, 5.4)

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

Revised: 9/2018

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**REFERENCES**

17. Vaginal Bleeding

17.2 Possible Serious Adverse Reactions with Estrogen-Alone Therapy

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

* Sections or subsections omitted from the full prescribing information are not listed.
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 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 WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of 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 Klaurosis 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.

2.1 Treatment of Atrophic Vaginitis and Klaurosis 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)].

2.2 Treatment 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 packaging: 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 receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).

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. 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 [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 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). 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.
associated with an increased risk of invasive breast cancer. 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 breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone users is the WHI substudy of daily CE (0.625 mg) -alone. 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[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 and more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Progestin use can reduce the risk of endometrial hyperplasia and endometrial cancer. 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 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 median 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[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 risk can persist beyond 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.

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[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, 1.21-3.49). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 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 ancillary 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 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 if there are other ocular signs suggestive of impending retinal vascular occlusion.

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

Women in 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 T₄ and T₃ 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 hyperparathyroidism 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 an 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, VII antigen, VII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antithrombin III, decreased antithrombin III activity; increased activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of fibrinogen and fibrinogen activity; increased plasminogen and antigen activity. Increased fibrinogen levels are found in patients with higher estrogen levels. 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.

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reactions 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.

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.

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, VII antigen, VII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antithrombin III, decreased antithrombin III activity; increased activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of fibrinogen and fibrinogen activity; increased plasminogen and antigen activity. Increased fibrinogen levels are found in patients with higher estrogen levels. 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.

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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.

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Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VII antigen, VII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antithrombin III, decreased antithrombin III activity; increased activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of fibrinogen and fibrinogen activity; increased plasminogen and antigen activity. Increased fibrinogen levels are found in patients with higher estrogen levels. 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.

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, fibrocytic 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.
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.

### 12.4 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.

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

<table>
<thead>
<tr>
<th>Pharmacokinetic Profiles of Unconjugated Estrogens</th>
<th>PREMARIN Vaginal Cream 0.5 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK Parameters Arithmetic Mean ± SD</td>
<td>C\text{max} (pg/mL)</td>
</tr>
<tr>
<td>Estrone</td>
<td>42.0 ± 13.9</td>
</tr>
<tr>
<td>Baseline-adjusted estrone</td>
<td>21.9 ± 13.1</td>
</tr>
<tr>
<td>Estradiol</td>
<td>12.8 ± 16.6</td>
</tr>
<tr>
<td>Baseline-adjusted estradiol</td>
<td>9.14 ± 14.7</td>
</tr>
</tbody>
</table>

**Pharmacokinetic Profiles of Conjugated Estrogens PREMARIN Vaginal Cream 0.5 g**

<table>
<thead>
<tr>
<th>PK Parameters Arithmetic Mean ± SD</th>
<th>C\text{max} (ng/mL)</th>
<th>T\text{max} (hr)</th>
<th>AUC\text{ss} (ng*hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total estrone</td>
<td>0.60 ± 0.32</td>
<td>6.0 ± 4.0</td>
<td>9.75 ± 4.99</td>
</tr>
<tr>
<td>Baseline-adjusted total estrone</td>
<td>0.40 ± 0.28</td>
<td>6.0 ± 4.0</td>
<td>5.79 ± 3.7</td>
</tr>
<tr>
<td>Total estradiol</td>
<td>0.04 ± 0.04</td>
<td>7.7 ± 5.9</td>
<td>0.70 ± 0.42</td>
</tr>
<tr>
<td>Baseline-adjusted total estradiol</td>
<td>0.04 ± 0.04</td>
<td>7.7 ± 6.0</td>
<td>0.49 ± 0.38</td>
</tr>
<tr>
<td>Total equilin</td>
<td>0.12 ± 0.15</td>
<td>6.1 ± 4.7</td>
<td>3.09 ± 1.37</td>
</tr>
</tbody>
</table>

**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.
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 57.4 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: 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

<table>
<thead>
<tr>
<th>Dyspareunia</th>
<th>PVC 0.5 g</th>
<th>Placebo 0.5 g</th>
<th>PVC 0.5 g 2x/wk</th>
<th>Placebo 0.5 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline n</td>
<td>50</td>
<td>18</td>
<td>52</td>
<td>21</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.26 (.99)</td>
<td>2.32 (.88)</td>
<td>2.43 (.76)</td>
<td>2.28 (1.04)</td>
</tr>
<tr>
<td>Week 12 n</td>
<td>50</td>
<td>18</td>
<td>52</td>
<td>21</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.77 (1.05)</td>
<td>1.93 (1.03)</td>
<td>0.88 (0.96)</td>
<td>1.63 (1.16)</td>
</tr>
<tr>
<td>Change from</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline to Week 12</td>
<td>-1.48 (1.17)</td>
<td>-0.40 (1.01)</td>
<td>-1.55 (0.92)</td>
<td>-0.62 (1.23)</td>
</tr>
<tr>
<td>P-value vs. Placebo</td>
<td>&lt;0.001 c</td>
<td>--</td>
<td>&lt;0.010 d</td>
<td>--</td>
</tr>
</tbody>
</table>

* PVC 21/7 = apply PVC for 21 days and then 7 days of no therapy
* PVC 2x/wk = apply PVC twice a week
* Comparison of PVC 21/7 with placebo 21/7
* Comparison of PVC 2x/wk with placebo 2x/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 colorectal cancer, 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

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE vs. Placebo (95% nCI)</th>
<th>CE n = 5,310</th>
<th>Placebo n = 5,429</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>0.95 (0.78–1.16)</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.91 (0.73–1.14)</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.01 (0.71–1.43)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>All Strokes</td>
<td>1.33 (1.05–1.68)</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.55 (1.19–2.01)</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.47 (1.06–2.06)</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.37 (0.90–2.07)</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>0.80 (0.62–1.04)</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.08 (0.75–1.55)</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.65 (0.45–0.94)</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>0.64 (0.44–0.93)</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Lower arm/wrist fractures</td>
<td>0.58 (0.47–0.72)</td>
<td>35</td>
<td>59</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.71 (0.64–0.80)</td>
<td>144</td>
<td>197</td>
</tr>
<tr>
<td>Death due to other causes</td>
<td>1.08 (0.88–1.32)</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>1.04 (0.88–1.22)</td>
<td>79</td>
<td>75</td>
</tr>
<tr>
<td>Global index</td>
<td>1.02 (0.92–1.13)</td>
<td>206</td>
<td>201</td>
</tr>
</tbody>
</table>

* Adapted from various 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.
* 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. 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 to 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.

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\(^a,b\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE/MPA vs. Placebo (95% nCI)</th>
<th>Absolute Risk per 10,000 Women-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>1.23 (0.99–1.53)</td>
<td>41</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.28 (1.00–1.63)</td>
<td>31</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.10 (0.70–1.75)</td>
<td>8</td>
</tr>
<tr>
<td>All Strokes</td>
<td>1.31 (1.03–1.68)</td>
<td>33</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.44 (1.09–1.90)</td>
<td>26</td>
</tr>
<tr>
<td>Deep vein thrombosis(^c)</td>
<td>1.95 (1.43–2.67)</td>
<td>26</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.13 (1.45–3.11)</td>
<td>18</td>
</tr>
<tr>
<td>Invasive breast cancer(^d)</td>
<td>1.24 (1.01–1.54)</td>
<td>41</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.61 (0.42–0.87)</td>
<td>10</td>
</tr>
<tr>
<td>Endometrial cancer(^e)</td>
<td>0.81 (0.48–1.36)</td>
<td>6</td>
</tr>
<tr>
<td>Cervical cancer(^f)</td>
<td>1.44 (0.47–4.42)</td>
<td>2</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.67 (0.47–0.96)</td>
<td>11</td>
</tr>
<tr>
<td>Vertebral fractures(^g)</td>
<td>0.65 (0.46–0.92)</td>
<td>11</td>
</tr>
<tr>
<td>Lower arm/wrist fractures(^h)</td>
<td>0.71 (0.59–0.85)</td>
<td>44</td>
</tr>
<tr>
<td>Total fractures(^i)</td>
<td>0.76 (0.69–0.83)</td>
<td>152</td>
</tr>
<tr>
<td>Overall Mortality(^i)</td>
<td>1.00 (0.83–1.19)</td>
<td>52</td>
</tr>
<tr>
<td>Global Index(^i)</td>
<td>1.13 (1.02–1.25)</td>
<td>184</td>
</tr>
</tbody>
</table>

\(^a\) Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
\(^b\) Results are based on centrally adjudicated data.
\(^c\) Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
\(^d\) Not included in “global index.”
\(^e\) Includes metastatic and non-metastatic breast cancer, with the exception of in situ cancer.
\(^f\) All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
\(^g\) 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% CI, 0.44–1.07)].

### 13.3 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)].
FDA-Approved Patient Labeling
PREMARIN® (prem-uh-rin)
(Conjugated estrogens) Vaginal Cream

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).
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).

**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, 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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