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

PREMARIN® (conjugated estrogens) tablets, for oral use
Initial U.S. Approval: 1942

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 (5.2)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.1)**
- **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 (5.3)**

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) (5.1)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)**
- **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 (5.3)**

INDICATIONS AND USAGE

PREMARIN is a mixture of estrogens indicated for:

- Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause (1.1)
- Treatment of Moderate to Severe Vulvar and Vaginal Atrophy due to Menopause (1.2)
- Treatment of Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure (1.3)
- Treatment of Breast Cancer (for Palliation Only) in Appropriately Selected Women and Men with Metastatic Disease (1.4)
- Treatment of Advanced Androgen-Dependent Carcinoma of the Prostate (for Palliation Only) (1.5)
- Prevention of Postmenopausal Osteoporosis (1.6)

DOSAGE AND ADMINISTRATION

- Daily administration of 0.3, 0.45, 0.625, 0.9, and 1.25 mg (2.1, 2.2, 2.3, 2.5, 2.6)
- Cyclic administration of 0.3, 0.625, and 1.25 mg (2.1, 2.2, 2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 0.3, 0.45, 0.625, 0.9, and 1.25 mg (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Breast cancer or history of breast cancer except in appropriately selected patients being treated for metastatic diseases (4, 5.2)
- Estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema with PREMARIN (5.7, 5.15)
- Hepatic impairment or disease (4, 5.11)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.10, 5.11)
- Monitor thyroid function in patients on thyroid replacement therapy (5.12, 5.19)

ADVERSE REACTIONS

Most common adverse reactions (≥5%) are: abdominal pain, asthenia, pain, back pain, headache, flatulence, nausea, depression, insomnia, breast pain, endometrial hyperplasia, leucorrhea, vaginal hemorrhage, and vaginitis. (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

- Lactation: Estrogen administration to lactating women has been shown to decrease the quantity and quality of breast milk (8.2)
- 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 (5.3, 8.5)

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

Revised: 4/2025

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FULL PRESCRIBING INFORMATION

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

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.2)].*

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.5, 14.6)].*

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) (0.625 mg)-alone, relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.5)].*

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 (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.6)].*

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 (5.1, 5.3), and Clinical Studies (14.5, 14.6)].*

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 (5.1), and Clinical Studies (14.5)].*

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.6)]*.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.2), and Clinical Studies (14.5)].*

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 Moderate to Severe Vasomotor Symptoms due to Menopause

1.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

Limitations of Use
When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, topical vaginal products should be considered.

1.3 Treatment of Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure

1.4 Treatment of Breast Cancer (for Palliation Only) in Appropriately Selected Women and Men with Metastatic Disease

1.5 Treatment of Advanced Androgen-Dependent Carcinoma of the Prostate (for Palliation Only)

1.6 Prevention of Postmenopausal Osteoporosis

Limitations of Use
When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medication should be carefully considered.

2 DOSAGE AND ADMINISTRATION

Generally, when estrogen therapy is prescribed for a postmenopausal woman with a uterus, a progestin should be considered to reduce the risk of endometrial cancer *[see Boxed Warning]*.

A woman without a uterus does not need progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.2, 5.16)]*.

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.

PREMARIN may be taken without regard to meals.

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Patients should be treated with the lowest effective dose. Generally, women should be started at 0.3 mg PREMARIN daily. Subsequent dosage adjustment may be made based upon the individual patient response. This dose should be periodically reassessed by the healthcare provider.

PREMARIN therapy may be given continuously, with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by 5 days off drug), as is medically appropriate on an individual basis.

2.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

Patients should be treated with the lowest effective dose. Generally, women should be started at 0.3 mg PREMARIN daily. Subsequent dosage adjustment may be made based upon the individual patient response. This dose should be periodically reassessed by the healthcare provider.

PREMARIN therapy may be given continuously, with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by 5 days off drug), as is medically appropriate on an individual basis.

2.3 Treatment of Hypoestrogenism due to Hypogonadism, Castration, or Primary Ovarian Failure

PREMARIN therapy should be initiated and maintained with the lowest effective dose to achieve clinical goals. Female hypogonadism: 0.3 mg or 0.625 mg daily, administered cyclically (e.g., three weeks on and one week off). Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium *[see Clinical Studies (14.4)]*.

Female castration or primary ovarian failure: 1.25 mg daily, cyclically. Adjust dosage, upward or downward, according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

2.4 Treatment of Breast Cancer (for Palliation Only) in Appropriately Selected Women and Men with Metastatic Disease

Suggested dosage is 10 mg three times daily, for a period of at least three months.

2.5 Treatment of Advanced Androgen-Dependent Carcinoma of the Prostate (for Palliation Only)

1.25 mg to 2 x 1.25 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.

2.6 Prevention of Postmenopausal Osteoporosis

PREMARIN therapy may be given continuously, with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by 5 days off drug), as is medically appropriate on an individual basis.

Patients should be treated with the lowest effective dose. Generally, women should be started at 0.3 mg PREMARIN daily. Subsequent dosage adjustment may be made based upon the individual clinical and bone mineral density responses. This dose should be periodically reassessed by the healthcare provider.

3 DOSAGE FORMS AND STRENGTHS

PREMARIN (conjugated estrogens tablets, USP)		
Tablet Strength	Tablet Shape/Color	Imprint
0.3 mg	oval/green	PREMARIN 0.3
0.45 mg	oval/blue	PREMARIN 0.45
0.625 mg	oval/maroon	PREMARIN 0.625
0.9 mg	oval/white	PREMARIN 0.9
1.25 mg	oval/yellow	PREMARIN 1.25

4 CONTRAINDICATIONS

PREMARIN therapy is contraindicated in individuals with any of the following conditions:

- Undiagnosed abnormal genital bleeding *[see Warnings and Precautions (5.2)]*
- Breast cancer or a history of breast cancer except in appropriately selected patients being treated for metastatic disease *[see Warnings and Precautions (5.2)]*
- Estrogen-dependent neoplasia *[see Warnings and Precautions (5.2)]*
- Active DVT, PE, or a history of these conditions *[see Warnings and Precautions (5.1)]*
- Active arterial thromboembolic disease (for example stroke and MI), or a history of these conditions *[see Warnings and Precautions (5.1)]*
- Known anaphylactic reaction or angioedema with PREMARIN *[see Warnings and Precautions (5.7, 5.15)]*
- Hepatic impairment or disease *[see Warnings and Precautions (5.11)]*
- Protein C, protein S or antithrombin deficiency, or other known thrombophilic disorders.

5 WARNINGS AND PRECAUTIONS

5.1 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 events 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 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 (14.5)]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

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

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.5)]*. The increase in risk was demonstrated after the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease
In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.5)]*.

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

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in Year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.5)]*.

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 CHD. There were more CHD events in the CE plus MPA-treated group than in the placebo group in Year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE (0.625 mg) plus MPA (2.5 mg) group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism (VTE)
In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE), was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3] *[see Clinical Studies (14.5)]*. 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 demonstrated during the first year and persisted[4] *[see Clinical Studies (14.5)]*. 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.

5.2 Malignant Neoplasms

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

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important.

Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer
The WHI substudy of daily CE (0.625 mg)-alone provided information about breast cancer in estrogen-alone users. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg)-alone was not associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*[5] *[see Clinical Studies (14.5)]*.

After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26% 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.[6]

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 (14.5)]*.

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

with estrogen plus progestin therapy. Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not 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 has been reported to result in an increase in abnormal mammograms, requiring further evaluation.

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

Ovarian Cancer

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

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

5.3 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% CI 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.6)]*.

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% CI 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.6)].*

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% CI 1.19-2.60). Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.6)]*.

5.4 Gallbladder Disease

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

5.5 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients 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.

5.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

5.7 Anaphylactic Reaction and Angioedema

Cases of anaphylaxis, which developed within minutes to hours after taking PREMARIN and require emergency medical management, have been reported in the postmarketing setting. Skin (hives, pruritis, 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, hands, and feet requiring medical intervention has occurred postmarketing in patients taking PREMARIN. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop an anaphylactic reaction with or without angioedema after treatment with PREMARIN should not receive PREMARIN again.

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 Exacerbation of Hypertriglyceridemia

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

5.11 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in patients 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 Exacerbation of Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

5.13 Fluid Retention

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

5.14 Hypocalcemia

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

5.15 Hereditary Angioedema

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

5.16 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.

5.17 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.

5.18 Laboratory Tests

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

Laboratory parameters may be useful in guiding dosage for the treatment of hypoestrogenism due to hypogonadism, castration and primary ovarian failure.

5.19 Drug-Laboratory Test Interactions

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

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

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

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

- Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Malignant Neoplasms *[see Boxed Warning, Warnings and Precautions (5.2)]*

6.1 Clinical Study Experience

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

During the first year of a 2-year clinical trial with 2,333 postmenopausal women with a uterus between 40 and 65 years of age (88% Caucasian), 1,012 women were treated with CE, and 332 were treated with placebo.

Table 1 summarizes treatment-related adverse reactions that occurred at a rate of ≥1% in any treatment group.

Table 1: Treatment-Related Adverse Reactions at a Frequency ≥1%

	PREMARIN 0.625 mg (n=348)	PREMARIN 0.45 mg (n=338)	PREMARIN 0.3 mg (n=326)	Placebo (n=332)
Body as a whole				
Abdominal pain	38 (11)	28 (8)	30 (9)	21 (6)
Asthenia	16 (5)	8 (2)	14 (4)	3 (1)
Back pain	18 (5)	11 (3)	13 (4)	4 (1)
Chest pain	2 (1)	3 (1)	4 (1)	2 (1)
Generalized edema	7 (2)	6 (2)	4 (1)	8 (2)
Headache	45 (13)	47 (14)	44 (13)	46 (14)
Moniliasis	5 (1)	4 (1)	4 (1)	1 (0)
Pain	17 (5)	10 (3)	12 (4)	14 (4)
Pelvic pain	10 (3)	9 (3)	8 (2)	4 (1)
Cardiovascular system				
Hypertension	4 (1)	4 (1)	7 (2)	5 (2)
Migraine	7 (2)	1 (0)	0	3 (1)
Palpitation	3 (1)	3 (1)	3 (1)	4 (1)
Vasodilatation	2 (1)	2 (1)	3 (1)	5 (2)
Digestive system				
Constipation	7 (2)	6 (2)	4 (1)	3 (1)
Diarrhea	4 (1)	5 (1)	5 (2)	8 (2)
Dyspepsia	7 (2)	5 (1)	6 (2)	14 (4)
Eructation	1 (0)	1 (0)	4 (1)	1 (0)
Flatulence	22 (6)	18 (5)	13 (4)	8 (2)
Increased appetite	4 (1)	1 (0)	1 (0)	2 (1)
Nausea	16 (5)	10 (3)	15 (5)	16 (5)
Metabolic and nutritional				
Hyperlipidemia	2 (1)	4 (1)	3 (1)	2 (1)
Peripheral edema	5 (1)	2 (1)	4 (1)	3 (1)
Weight gain	11 (3)	10 (3)	8 (2)	14 (4)
Musculoskeletal system				
Arthralgia	6 (2)	3 (1)	2 (1)	5 (2)
Leg cramps	10 (3)	5 (1)	9 (3)	4 (1)
Myalgia	2 (1)	1 (0)	4 (1)	1 (0)
Nervous system				
Anxiety	6 (2)	4 (1)	2 (1)	4 (1)
Depression	17 (5)	15 (4)	10 (3)	17 (5)
Dizziness	9 (3)	7 (2)	4 (1)	5 (2)
Emotional lability	3 (1)	4 (1)	5 (2)	8 (2)
Hypertonia	1 (0)	1 (0)	5 (2)	3 (1)
Insomnia	16 (5)	10 (3)	13 (4)	14 (4)
Nervousness	9 (3)	12 (4)	2 (1)	6 (2)
Skin and appendages				
Acne	3 (1)	1 (0)	8 (2)	3 (1)
Alopecia	6 (2)	6 (2)	5 (2)	2 (1)
Hirsutism	4 (1)	2 (1)	1 (0)	0
Pruritus	11 (3)	11 (3)	10 (3)	3 (1)
Rash	6 (2)	3 (1)	1 (0)	2 (1)
Skin discoloration	4 (1)	2 (1)	0	1 (0)
Sweating	4 (1)	1 (0)	3 (1)	4 (1)

Table 1: Treatment-Related Adverse Reactions at a Frequency ≥1%

	PREMARIN 0.625 mg (n=348)	PREMARIN 0.45 mg (n=338)	PREMARIN 0.3 mg (n=326)	Placebo (n=332)
Urogenital system				
Breast disorder	6 (2)	3 (1)	3 (1)	6 (2)
Breast enlargement	3 (1)	4 (1)	7 (2)	3 (1)
Breast neoplasm	4 (1)	4 (1)	7 (2)	7 (2)
Breast pain	37 (11)	39 (12)	24 (7)	26 (8)
Cervix disorder	8 (2)	4 (1)	5 (2)	0
Dysmenorrhea	12 (3)	10 (3)	4 (1)	2 (1)
Endometrial disorder	4 (1)	2 (1)	2 (1)	0
Endometrial hyperplasia	16 (5)	8 (2)	1 (0)	0
Leukorrhea	17 (5)	17 (5)	12 (4)	6 (2)
Metrorrhagia	11 (3)	4 (1)	3 (1)	1 (0)
Urinary tract infection	1 (0)	2 (1)	1 (0)	4 (1)
Uterine fibroids enlarged	6 (2)	1 (0)	2 (1)	2 (1)
Uterine spasm	11 (3)	5 (1)	3 (1)	2 (1)
Vaginal dryness	1 (0)	2 (1)	1 (0)	6 (2)
Vaginal hemorrhage	46 (13)	13 (4)	6 (2)	0
Vaginal moniliasis	14 (4)	10 (3)	12 (4)	5 (2)
Vaginitis	18 (5)	7 (2)	9 (3)	1 (0)

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of PREMARIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible always to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary system
Abnormal uterine bleeding; dysmenorrheal or pelvic pain, increase in size of uterine leiomyomata, vaginitis, including vaginal candidiasis, change in cervical secretion, ovarian cancer, endometrial hyperplasia, endometrial cancer, leukorrhea.

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

Cardiovascular
Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

Gastrointestinal
Nausea, vomiting, abdominal pain, bloating, cholestatic jaundice, increased incidence of gallbladder disease, pancreatitis, enlargement of hepatic hemangiomas, ischemic colitis.

Skin
Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, loss of scalp hair, hirsutism, pruritus, rash.

Eyes
Retinal vascular thrombosis, intolerance to contact lenses.

Central nervous system
Headache, migraine, dizziness , mental depression, nervousness, mood disturbances, irritability, exacerbation of epilepsy, dementia, possible growth potentiation of benign meningioma.

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

7 DRUG INTERACTIONS

Data from a single-dose drug-drug interaction study involving CE and MPA indicate that the pharmacokinetic disposition of both drugs is not altered when the drugs are coadministered. No other clinical drug-drug interaction studies have been conducted with CE.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
PREMARIN is not indicated for use during pregnancy.

There are no data with the use of PREMARIN tablet in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives (estrogen and progestins) before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary
Estrogens and progestins and metabolites are present in human milk. These hormones can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for PREMARIN and any potential adverse effects on the breast-fed child from PREMARIN or from the underlying maternal condition.

8.4 Pediatric Use

Estrogen therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding. In boys, estrogen treatment may modify the normal pubertal process and induce gynecomastia.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in studies utilizing PREMARIN to determine whether those over 65 years of age differ from younger subjects in their response to PREMARIN.

The Women's Health Initiative Study
In the WHI estrogen-alone substudy (daily CE 0.625 mg-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.5)]*.

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.5)]*.

The Women's Health Initiative Memory Study
In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions (5.3), and Clinical Studies (14.6)]*.

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Warnings and Precautions (5.3), and Clinical Studies (14.6)]*.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

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

11 DESCRIPTION

PREMARIN® (conjugated estrogens tablets, USP) for oral administration contains a mixture of CE purified from pregnant mares' urine and consists of 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 concomitant components as sodium sulfate conjugates, 17α-dihydroequilin, 17α estradiol, and 17β-dihydroequilin. Tablets for oral administration are available in 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg strengths of CE.

PREMARIN 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg tablets also contain the following inactive ingredients: calcium phosphate tribasic, carnauba wax, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, powdered cellulose, sucrose, and titanium dioxide. Each tablet strength contains the following colors:

Tablet strength	Tablet color contains
0.3 mg	D&C Yellow No. 10 and FD&C Blue No. 2
0.45 mg	FD&C Blue No. 2
0.625 mg	FD&C Blue No. 2 and FD&C Red No. 40
0.9 mg	D&C Red No. 30 and D&C Red No. 7
1.25 mg	Black iron oxide, D&C Yellow No. 10 and FD&C Yellow No. 6

PREMARIN tablets comply with USP Dissolution Test criteria, as outlined below:

PREMARIN 1.25 mg tablets	USP Dissolution Test 4
PREMARIN 0.3 mg, 0.45 mg and 0.625 mg tablets	USP Dissolution Test 5
PREMARIN 0.9 mg tablets	USP Dissolution Test 6

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, 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

There are no pharmacodynamic data for PREMARIN.

12.3 Pharmacokinetics

Absorption

Conjugated estrogens are water-soluble and are absorbed from the gastrointestinal tract after release from the drug formulation. The PREMARIN tablet releases CE slowly over several hours. Table 2 summarizes the mean pharmacokinetic parameters for unconjugated and CE following administration of 1 x 0.625 mg and 1 x 1.25 mg tablets to healthy postmenopausal women.

Food effect: The pharmacokinetics of PREMARIN 0.45 mg and 1.25 mg tablets were assessed following a single dose with a high-fat breakfast and with fasting administration. The C_{max} and AUC of estrogens were altered approximately 3-13%. The changes to C_{max} and AUC are not considered clinically meaningful, therefore PREMARIN may be taken without regard to meals.

Table 2: Pharmacokinetic Parameters for PREMARIN

Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 1 x 0.625 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	87 (33)	9.6 (33)	50.7 (35)	5557 (59)
Baseline-adjusted estrone	64 (42)	9.6 (33)	20.2 (40)	1723 (52)
Equilin	31 (38)	7.9 (32)	12.9 (112)	602 (54)
Pharmacokinetic Profile of CE Following a Dose of 1 x 0.625 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Total Estrone	2.7 (43)	6.9 (25)	26.7 (33)	75 (52)
Baseline-adjusted total estrone	2.5 (45)	6.9 (25)	14.8 (35)	46 (48)
Total Equilin	1.8 (56)	5.6 (45)	11.4 (31)	27 (56)
Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 1 x 1.25 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	124 (30)	10.0 (32)	38.1 (37)	6332 (44)
Baseline-adjusted estrone	102 (35)	10.0 (32)	19.7 (48)	3159 (53)
Equilin	59 (43)	8.8 (36)	10.9 (47)	1182 (42)
Pharmacokinetic Profile of CE Following a Dose of 1 x 1.25 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Total Estrone	4.5 (39)	8.2 (58)	26.5 (40)	109 (46)
Baseline-adjusted total estrone	4.3 (41)	8.2 (58)	17.5 (41)	87 (44)
Total equilin	2.9 (42)	6.8 (49)	12.5 (34)	48 (51)

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 proportion of the circulating estrogens exist 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 with PREMARIN 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 *[see Warnings and Precautions (5.2)]*.

14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2,805 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups of either placebo or CE, with or without MPA. Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least seven moderate to severe hot flushes daily, or at least 50 moderate to severe hot flushes during the week before randomization. PREMARIN (0.3 mg, 0.45 mg, and 0.625 mg tablets) was shown to be statistically better than placebo at weeks 4 and 12 for relief of both frequency and severity of moderate to severe vasomotor symptoms. Table 3 shows the adjusted mean number of hot flushes in the PREMARIN 0.3 mg, 0.45 mg, and 0.625 mg and placebo groups during the initial 12-week period.

Table 3: Summary Tabulation of the Number of Hot Flushes Per Day – Mean Values and Comparisons Between the Active Treatment Groups and the Placebo Group: Patients with at Least 7 Moderate to Severe Flushes Per Day or at Least 50 Per Week at Baseline, Last Observation Carried Forward (LOCF)

Treatment (No. of Patients)	----------No. of Hot Flushes/Day----------			
Time Period (week)	Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SD	p-Values vs Placebo[a]
0.625 mg CE (n = 27)				
4	12.29 ± 3.89	1.95 ± 2.77	-10.34 ± 4.73	<0.001
12	12.29 ± 3.89	0.75 ± 1.82	-11.54 ± 4.62	<0.001
0.45 mg CE (n = 32)				
4	12.25 ± 5.04	5.04 ± 5.31	-7.21 ± 4.75	<0.001
12	12.25 ± 5.04	2.32 ± 3.32	-9.93 ± 4.64	<0.001

Table 3: Summary Tabulation of the Number of Hot Flushes Per Day – Mean Values and Comparisons Between the Active Treatment Groups and the Placebo Group: Patients with at Least 7 Moderate to Severe Flushes Per Day or at Least 50 Per Week at Baseline, Last Observation Carried Forward (LOCF)

Treatment (No. of Patients)	----------No. of Hot Flushes/Day----------			
0.3 mg CE (n = 30)				
4	13.77 ± 4.78	4.65 ± 3.71	-9.12 ± 4.71	<0.001
12	13.77 ± 4.78	2.52 ± 3.23	-11.25 ± 4.60	<0.001
Placebo (n = 28)				
4	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 4.71	-
12	11.69 ± 3.87	5.71 ± 5.22	-5.98 ± 4.60	-
[a] Based on analysis of covariance with treatment as factor and baseline as covariate.				

14.2 Effects on Vulvar and Vaginal Atrophy

Results of vaginal maturation indexes at cycles 6 and 13 showed that the differences from placebo were statistically significant ($p < 0.001$) for all treatment groups. (CE alone and CE/MPA treatment groups).

14.3 Effects on Bone Mineral Density

Health and Osteoporosis, Progestin and Estrogen (HOPE) Study
The HOPE study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy postmenopausal women with an intact uterus. Subjects (mean age 53.3 ± 4.9 years) were 2.3 ± 0.9 years on average since menopause and took one 600 mg tablet of elemental calcium (Caltrate™) daily.

Subjects were not given Vitamin D supplements. They were treated with PREMARIN 0.625 mg, 0.45 mg, 0.3 mg, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L_2 to L_4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

Intent-to-treat subjects
All active treatment groups showed significant differences from placebo in each of the four BMD endpoints at cycles 6, 13, 19, and 26. The mean percent increases in the primary efficacy measure (L_2 to L_4 BMD) at the final on-therapy evaluation (cycle 26 for those who completed and the last available evaluation for those who discontinued early) were 2.46% with 0.625 mg, 2.26% with 0.45 mg, and 1.13% with 0.3 mg. The placebo group showed a mean percent decrease from baseline at the final evaluation of 2.45%. These results show that the lower dosages of PREMARIN were effective in increasing L_2 to L_4 BMD compared with placebo, and therefore support the efficacy of the lower doses.

The analysis for the other three BMD endpoints yielded mean percent changes from baseline in femoral trochanter that were generally larger than those seen for L_2 to L_4, and changes in femoral neck and total body that were generally smaller than those seen for L_2 to L_4. Significant differences between groups indicated that each of the PREMARIN treatments was more effective than placebo for all three of these additional BMD endpoints. With regard to femoral neck and total body, the active treatment groups all showed mean percent increases in BMD, while placebo treatment was accompanied by mean percent decreases. For femoral trochanter, each of the PREMARIN dose groups showed a mean percent increase that was significantly greater than the small increase seen in the placebo group. The percent changes from baseline to final evaluation are shown in Table 4.

Table 4: Percent Change in Bone Mineral Density: Comparison Between Active and Placebo Groups in the Intent-to-Treat Population, LOCF

Region Evaluated Treatment Group[a]	No. of Subjects	Baseline (g/cm^2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs. Placebo
L_2 to L_4 BMD				
0.625	83	1.17 ± 0.15	2.46 ± 0.37	<0.001
0.45	91	1.13 ± 0.15	2.26 ± 0.35	<0.001
0.3	87	1.14 ± 0.15	1.13 ± 0.36	<0.001
Placebo	85	1.14 ± 0.14	-2.45 ± 0.36	
Total Body BMD				
0.625	84	1.15 ± 0.08	0.68 ± 0.17	<0.001
0.45	91	1.14 ± 0.08	0.74 ± 0.16	<0.001
0.3	87	1.14 ± 0.07	0.40 ± 0.17	<0.001
Placebo	85	1.13 ± 0.08	-1.50 ± 0.17	
Femoral Neck BMD				
0.625	84	0.91 ± 0.14	1.82 ± 0.45	<0.001
0.45	91	0.89 ± 0.13	1.84 ± 0.44	<0.001
0.3	87	0.86 ± 0.11	0.62 ± 0.45	<0.001
Placebo	85	0.88 ± 0.14	-1.72 ± 0.45	
Femoral Trochanter BMD				
0.625	84	0.78 ± 0.13	3.82 ± 0.58	<0.001
0.45	91	0.76 ± 0.12	3.16 ± 0.56	0.003
0.3	87	0.75 ± 0.10	3.05 ± 0.57	0.005
Placebo	85	0.75 ± 0.12	0.81 ± 0.58	

[a] Identified by dosage (mg) of PREMARIN or placebo.

Figure 1 shows the cumulative percentage of subjects with changes from baseline equal to or greater than the value shown on the x-axis.

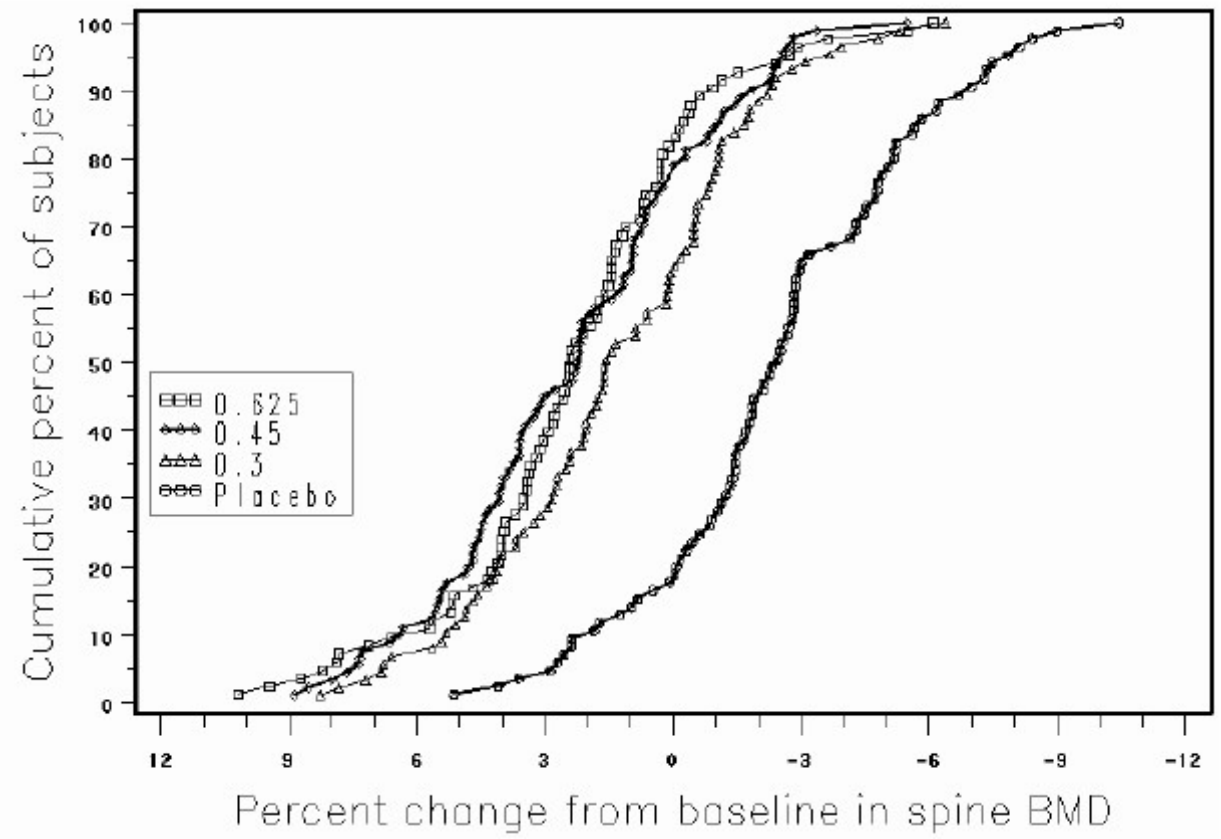


Figure 1. Cumulative Percent of Subjects With Changes From Baseline in Spine BMD of Given Magnitude or Greater in PREMARIN® and Placebo Groups

The mean percent changes from baseline in L_2 to L_4 BMD for women who completed the bone density study are shown with standard error bars by treatment group in Figure 2. Significant differences between each of the PREMARIN dosage groups and placebo were found at cycles 6, 13, 19, and 26.

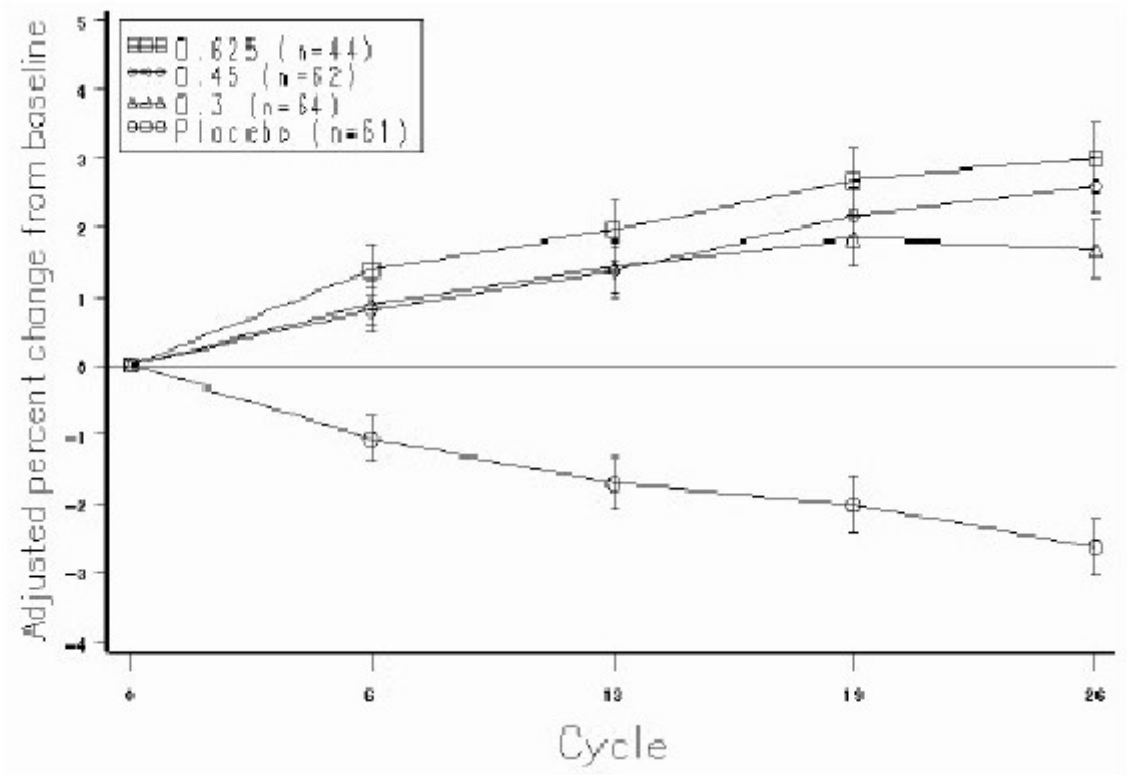


Figure 2. Adjusted Mean (SE) Percent Change From Baseline at Each Cycle in Spine BMD: Subjects Completing in PREMARIN Groups and Placebo

The bone turnover markers, serum osteocalcin and urinary N-telopeptide, significantly decreased ($p < 0.001$) in all active-treatment groups at cycles 6, 13, 19, and 26 compared with the placebo group. Larger mean decreases from baseline were seen with the active groups than with the placebo group. Significant differences from placebo were seen less frequently in urine calcium.

14.4 Effects on Female Hypogonadism

In clinical studies of delayed puberty due to female hypogonadism, breast development was induced by doses as low as 0.15 mg. The dosage may be gradually titrated upward at 6-to 12 month intervals as needed to achieve appropriate bone age advancement and eventual epiphyseal closure. Clinical studies suggest that doses of 0.15 mg, 0.3 mg, and 0.6 mg are associated with mean ratios of bone age advancement to chronological age progression ($\Delta BA/\Delta CA$) of 1.1, 1.5, and 2.1, respectively. (PREMARIN in the dose strength of 0.15 mg is not available commercially). Available data suggest that chronic dosing with 0.625 mg is sufficient to induce artificial cyclic menses with sequential progestin treatment and to maintain bone mineral density after skeletal maturity is achieved.

14.5 Women's Health Initiative Studies

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

WHI Estrogen-Alone Substudy

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

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other) after an average follow-up of 7.1 years, are presented in Table 5.

Table 5: Relative and Absolute Risk Seen in the Estrogen Alone Substudy of WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[b])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78–1.16)	54	57
Non-fatal MI[c]	*0.91 (0.73–1.14)*	*40*	*43*
CHD death[c]	*1.01 (0.71–1.43)*	*16*	*16*
All Stroke[c]	1.33 (1.05–1.68)	45	33
Ischemic stroke[c]	*1.55 (1.19–2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06–2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90–2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62–1.04)	28	34
Colorectal cancer[e]	1.08 (0.75–1.55)	17	16
Hip fracture[c]	0.65 (0.45–0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44–0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47–0.72)	35	59
Total fractures[c,d]	0.71 (0.64–0.80)	144	197
Death due to other causes[e,f]	1.08 (0.88–1.32)	53	50
Overall mortality[c,d]	1.04 (0.88–1.22)	79	75
Global Index[g]	1.02 (0.92–1.13)	206	201

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[c] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[d] Not included in "global index."
[e] Results are based on an average follow-up of 6.8 years.
[f] All deaths, except from breast or colorectal cancer, definite/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.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.[9] The absolute excess risk of events

included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow up of 7.1 years. See Table 5.

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

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50-59 years of age, a non-significant trend toward reduced risk for CHD *[hazard ratio (HR) 0.63 (95% CI 0.36-1.09)]* and overall mortality *[HR 0.71 (95% 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 estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9% White, 6.8% Black, 5.4% Hispanic, 3.9% Other) are presented in Table 6. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 6: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]

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

Cervical cancer[d]	1.44 (0.47–4.42)	2	1
Hip fracture	0.67 (0.47–0.96)	11	16
Vertebral fractures[d]	0.65 (0.46–0.92)	11	17
Lower arm/wrist fractures[d]	0.71 (0.59–0.85)	44	62
Total fractures[d]	0.76 (0.69–0.83)	152	199
Overall Mortality[f]	1.00 (0.83–1.19)	52	52
Global Index[g]	1.13 (1.02–1.25)	184	165

[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 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 50-59 years of age, a non-significant trend toward reduced risk for overall mortality *[HR 0.69 (95% CI 0.44-1.07)]*.

14.6 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 (45% were 65 to 69 years of age; 36% were 70 to 74 years of age; 19% 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% 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 groups 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 (5.3*), *and Use in Specific Populations* (*8.5)]*.

The WHIMS estrogen plus progestin ancillary study enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were 65 to 69 years of age; 35% were 70 to 74 years; 18% 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 was 2.05 (95% CI, 1.21–3.48). The absolute risk of probable dementia for CE (0.625 mg) plus MPA (2.5 mg) 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 both the treatment and placebo groups 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 (5.3), 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% 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 (5.3), and Use in Specific Populations (8.5)]*.

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PREMARIN® (conjugated estrogens tablets, USP)

- Each oval green tablet contains 0.3 mg, in bottles of 100 (NDC 0046-1100-81) and 1,000 (NDC 0046-1100-91).
- Each oval blue tablet contains 0.45 mg, in bottles of 100 (NDC 0046-1101-81).
- Each oval maroon tablet contains 0.625 mg, in bottles of 100 (NDC 0046-1102-81) and 1,000 (NDC 0046-1102-91).
- Each oval white tablet contains 0.9 mg, in bottles of 100 (NDC 0046-1103-81).
- Each oval yellow tablet contains 1.25 mg, in bottles of 100 (NDC 0046-1104-81) and 1,000 (NDC 0046 1104-91).

The appearance of these tablets is a trademark of Wyeth LLC.

16.2 Storage and Handling

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

Dispense in a well-closed container, as defined in the USP.

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Patient Information).

17.1 Vaginal Bleeding

Inform postmenopausal women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.2)]*.

17.2 Possible Serious Adverse Reactions with Estrogens

Inform postmenopausal women of possible serious adverse reactions of estrogen therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

17.3 Possible Less Serious but Common Adverse Reactions with Estrogens

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

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

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LAB-0467-8.2a

PATIENT INFORMATION

PREMARIN®(prem-uh-rin)

(Conjugated estrogen tablets)

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

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT PREMARIN (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 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 the cause.
- **Do not use estrogen-alone to prevent heart disease, heart attacks, or dementia (decline of 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 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 65 years of age or older**
- **You and your healthcare provider should talk regularly about whether you still need treatment with PREMARIN**

What is PREMARIN?

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

What is PREMARIN used for?

PREMARIN is used after menopause to:

- **Reduce moderate to severe hot flushes**

  Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

  When the estrogen levels begin dropping, some women get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot

flushes"). In some women the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe.

- **Treat menopausal changes in and around the vagina**
  You and your healthcare provider should talk regularly about whether you still need treatment with PREMARIN to control these problems. If you use PREMARIN only to treat your menopausal changes in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

- **Help reduce your chances of getting osteoporosis (thin weak bones)**
  Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use PREMARIN only to prevent osteoporosis due to menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

  Weight-bearing exercise, like walking or running, and taking calcium (1500 mg/day of elemental calcium) and vitamin D (400-800 IU/day) supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

  You and your healthcare provider should talk regularly about whether you still need treatment with PREMARIN.

PREMARIN is also used to:

- Treat certain conditions in women before menopause if their ovaries do not make enough estrogen naturally.
- Ease symptoms of certain cancers that have spread through the body, in men and women

Who should not take PREMARIN?

Do not take PREMARIN 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.
- **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 or any of its ingredients**
  See the end of this leaflet for a list of ingredients in PREMARIN.

Tell your healthcare provider

- **If you have any 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, 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 works. PREMARIN 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 taking PREMARIN.

- **If you are pregnant or think you may be pregnant**
  PREMARIN is not for pregnant women.

- **If you are breastfeeding**
  The hormones in PREMARIN can pass into your breast milk.

How should I take PREMARIN?

- Take one PREMARIN tablet at the same time each day
- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.
- 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.
- If you see something that resembles a tablet in your stool, talk to your healthcare provider.
- Take PREMARIN with or without food.

What are the possible side effects of PREMARIN?

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
- Breast cancer
- Cancer of the lining of the uterus (womb)
- Cancer of the ovary

- Dementia
- High or low blood calcium
- Gallbladder disease
- Visual abnormalities
- High blood pressure
- High levels of fat (triglycerides) in your blood
- Liver problems
- Changes in your thyroid hormone levels
- Fluid retention
- Cancer changes of endometriosis
- Enlargement of benign tumors of the uterus ("fibroids")
- Severe allergic reactions
- Changes in certain laboratory test results, such as high blood sugar

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
- Swelling of the face, lips, and tongue with or without red itchy bumps

Common side effects of PREMARIN include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps/bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

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

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

- Talk with your healthcare provider regularly about whether you should continue taking PREMARIN
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the uterus (womb).
- See your health care provider right away if you get vaginal bleeding while taking PREMARIN
- 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 of getting heart disease.

General information about the safe and effective use of PREMARIN

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

Keep PREMARIN out of the reach of children

This leaflet provides a summary of the most important information about PREMARIN. If you would like more information, talk with your healthcare provider or pharmacist.

What are the ingredients in PREMARIN?

PREMARIN contains a mixture of conjugated estrogens, which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin.

PREMARIN 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg tablets also contain the following inactive ingredients: calcium phosphate tribasic, hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, sucrose and titanium dioxide.

The tablets come in different strengths and each strength tablet is a different color. The color ingredients are:

- 0.3 mg tablet (green color): D&C Yellow No. 10 and FD&C Blue No. 2.
- 0.45 mg tablet (blue color): FD&C Blue No. 2.
- 0.625 mg tablet (maroon color): FD&C Blue No. 2 and FD&C Red No. 40.
- 0.9 mg tablet (white color): D&C Red No. 30 and D&C Red No. 7.
- 1.25 mg tablet (yellow color): black iron oxide, D&C Yellow No. 10, and FD&C Yellow No. 6.

The appearance of these tablets is a trademark of Wyeth LLC.

Store at Controlled Room Temperature 20° – 25°C (68° – 77°F).

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

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