# PREMARIN® TABLETS
# (Conjugated estrogens)

**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 (13.5, 13.6)]*.**

**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 (13.5)]*.**

**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 (8.4), and Clinical Studies (13.6)]*.**

**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 (13.5, 13.6)]*.**

**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 (13.5)]*.**

**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 (8.4), and Clinical Studies (13.6)]*.**

**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 (13.5)]*.**

**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 (13.4)]*.

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® tablet (conjugated estrogens)

| Tablet Strength | Tablet Shape/Color | Imprint |
|---|---|---|
| 0.3 mg | oval/green | PREMARIN<br>0.3 |
| 0.625 mg | oval/maroon | PREMARIN<br>0.625 |

## 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 (13.5)]*. 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 (13.5)]*. 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 (13.5)]*.

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 (13.5)]*.

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***

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 (13.5)]*. 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 (13.5)]*. 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 overall evidence shows an increased risk of breast cancer in women taking combined estrogen-progestogen or estrogen-only HRT that is dependent on the duration of taking HRT.

The Women's Health Initiative trial (WHI) found no increase in the risk of breast cancer in hysterectomized women using estrogen-only HRT. 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 (13.5)]*.

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 (13.5)]*.

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.

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms, which may adversely affect the radiological detection of breast cancer, 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% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

**5.3 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 (8.4), and Clinical Studies (13.6)]*.

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 (8.4), and Clinical Studies (13.6)]*.

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 (8.4), and Clinical Studies (13.6)]*.

### 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 post-marketing 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, hands, and feet requiring medical intervention has occurred post-marketing 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 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 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), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 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) |

**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)** |
|---|---|---|---|---|
| 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) |
| ***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) |

**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)** |
|---|---|---|---|---|
| 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 Post-marketing 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.

***Breast Cancer Risk***
An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestogen therapy for more than 5 years.

The increased risk in users of estrogen-only therapy is lower than that seen in users of estrogen-progestogen combinations.

The level of risk is dependent on the duration of use.

Absolute risk estimations based on results of the largest randomized placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented.

Largest meta-analysis of prospective epidemiological studies.

Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 ($kg/m^2$).

| **Age at start HRT (years)** | **Incidence per 1,000 never-users of HRT over a 5-year period (50-54 years) *** | **Risk ratio** | **Additional cases per 1,000 HRT users after 5 years** |
|---|---|---|---|
| Estrogen-only HRT | | | |
| 50 | 13.3 | 1.2 | 2.7 |
| Combined estrogen-progestogen | | | |
| 50 | 13.3 | 1.6 | 8.0 |

* Taken from baseline incidence rates in England in 2015 in women with BMI 27 ($kg/m^2$).

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 ($kg/m^2$).

| **Age at start HRT (years)** | **Incidence per 1,000 never-users of HRT over a 10-year period (50-59 years) *** | **Risk ratio** | **Additional cases per 1,000 HRT users after 10 years** |
|---|---|---|---|
| Estrogen-only HRT | | | |
| 50 | 26.6 | 1.3 | 7.1 |
| Combined estrogen-progestogen | | | |
| 50 | 26.6 | 1.8 | 20.8 |

* Taken from baseline incidence rates in England in 2015 in women with BMI 27 ($kg/m^2$).

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

US WHI Studies-additional risk of breast cancer after 5 years' use

| Age range (years) | Incidence per 1,000 women in placebo arm over 5 years | Risk ratio & 95% CI | Additional cases per 1,000 HRT users over 5 years (95% CI) |
|---|---|---|---|
| CEE estrogen-only | | | |
| 50-79 | 21 | 0.8 (0.7-1.0) | -4 (-6-0) * |
| CEE+MPA estrogen & progestogen** | | | |
| 50-79 | 17 | 1.2 (1.0-1.5) | 4 (0-9) |

* WHI study in women with no uterus, which did not show an increase in risk of breast cancer.
** When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

## 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 co-administered. 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.

**8.3 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.

**8.4 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 (13.5)]*.

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 (13.5)]*.

***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 (13.6)]*.

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 (13.6)]*.

### 8.5 Renal Impairment

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

### 8.6 Hepatic Impairment

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

## 9 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.

## 10 DESCRIPTION

PREMARIN tablets (conjugated estrogens) 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, 0.625 mg strengths of CE.

PREMARIN tablets 0.3 mg, 0.625 mg 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.

## 11 CLINICAL PHARMACOLOGY

### 11.1 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.

### 11.2 Pharmacodynamics

There are no pharmacodynamic data for PREMARIN.

### 11.3 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 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 with PREMARIN in specific populations, including patients with renal or hepatic impairment.

## 12 NONCLINICAL TOXICOLOGY

### 12.1 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)]*.

## 13 CLINICAL STUDIES

### 13.1 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 |
| 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.

### 13.2 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).

### 13.3 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** |
|---|---|---|---|---|
| L2 to L4 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.

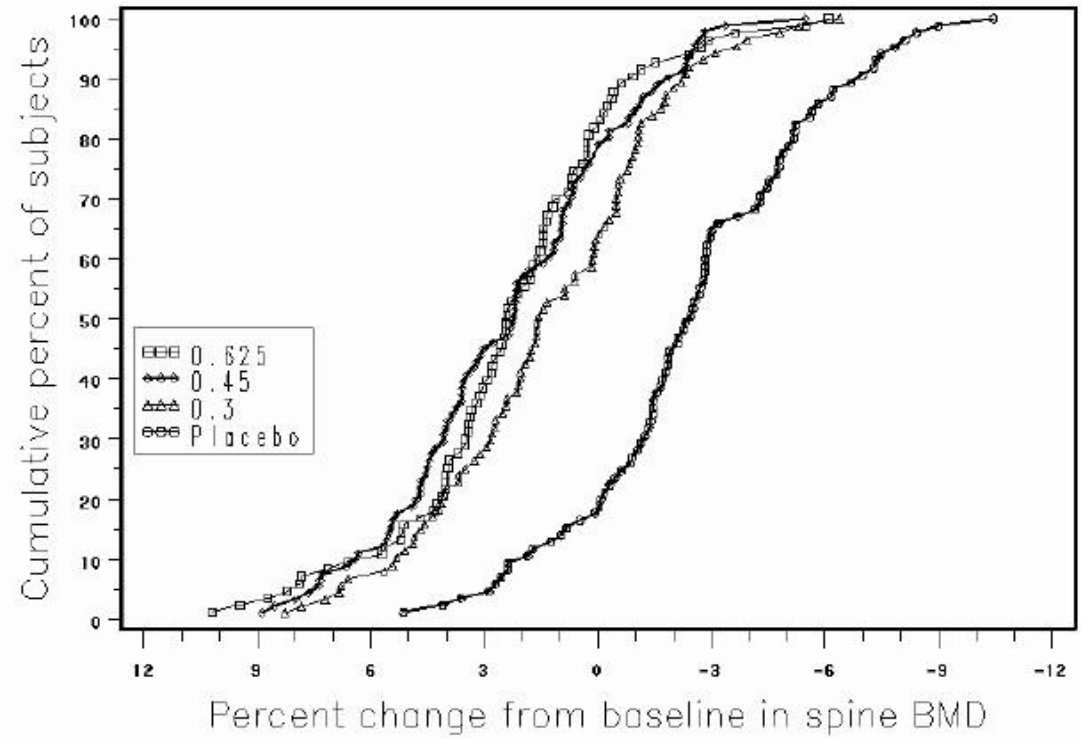



**Figure 1. Cumulative Percent of Subjects with Changes from Baseline in Spine BMD of Given Magnitude or Greater in PREMARIN and Placebo Groups**

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.

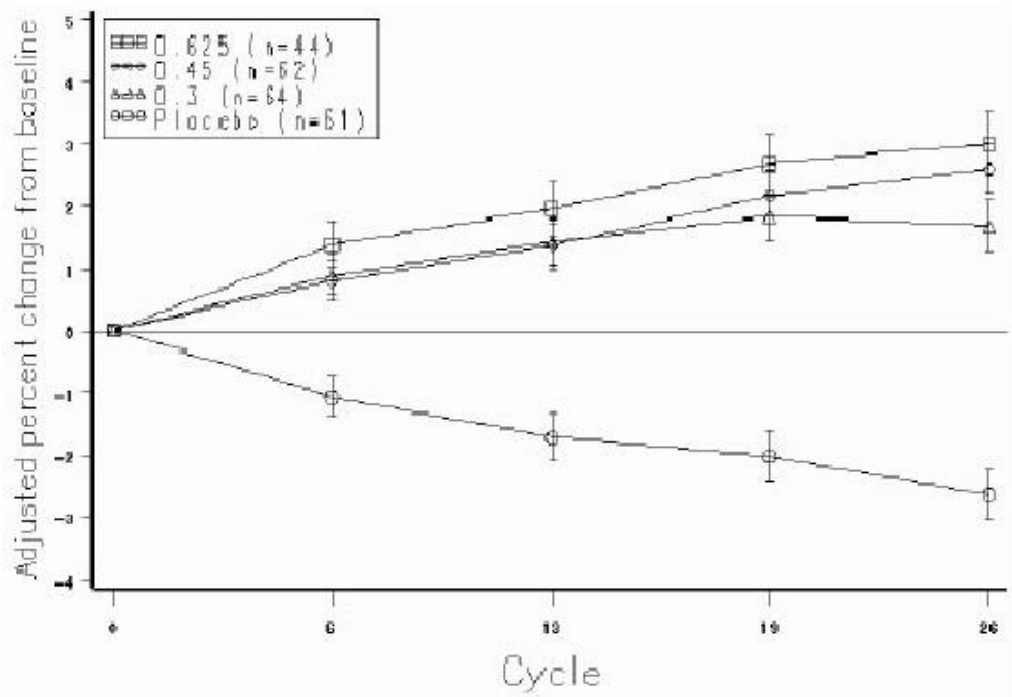



**Figure 2. Adjusted Mean (SE) Percent Change From Baseline at Each Cycle in Spine BMD: Subjects Completing in PREMARIN Groups and Placebo**

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.

### 13.4 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.

### 13.5 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 MIc* | *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)]*.

### 13.6 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* (*8.4)]*.

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 (8.4)]*.

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 (8.4)]*.

## 14 REFERENCES


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5. Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy. *JAMA*. 2006;295:1647-1657.
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8. Shumaker SA, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. JAMA. 2004;291:2947-2958.
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10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation*. 2006;113:2425-2434.


## 15 STORAGE AND HANDLING

Please refer to the outer packaging for the storage condition.

## 16 PATIENT COUNSELING INFORMATION

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

### 16.1 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)]*.

**16.2 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)]*.

**16.3 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.

Pfizer Corporation Hong Kong Limited
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