NEED HELP DIALING DOWN HOT FLASHES?

PREMARIN is a treatment for moderate to severe hot flashes due to menopause.

IMPORTANT SAFETY INFORMATION

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 out the cause.

Do not use estrogens with or without progestins to prevent heart disease, heart attacks, strokes or dementia (decline in brain function).

Using estrogen-alone may increase your chances of getting strokes or blood clots. Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.

Using estrogens, with or without progestins, may increase your chance of getting dementia, based on a study of women 65 years of age or older.

Estrogens should be used at the lowest dose possible, only for as long as needed. You and your healthcare provider should talk regularly about whether you still need treatment.

PREMARIN should not be used if you have unusual vaginal bleeding, have or had cancer, had a stroke or heart attack, have or had blood clots or liver problems, have a bleeding disorder, are allergic to any of its ingredients, or think you may be pregnant. In general, the addition of a progestin is recommended for women with a uterus to reduce the chance of getting cancer of the uterus.

Estrogens increase the risk of gallbladder disease. Discontinue estrogen if loss of vision, pancreatitis, or liver problems occur. If you take thyroid medication, consult your healthcare provider, as use of estrogens may change the amount needed.

The most common (≥5%) side effects are abdominal pain, asthenia, pain, back pain, headache, flatulence, nausea, depression, insomnia, breast pain, endometrial hyperplasia, leucorrhea, vaginal hemorrhage, and vaginitis.

INDICATION

PREMARIN is used after menopause to reduce moderate to severe hot flashes.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying full Prescribing Information, including BOXED WARNING and Patient Information.

www.PREMARIN.com
WHAT SHOULD I KNOW ABOUT HOT FLASHES?

YOU’RE NOT ALONE.

Up to 80% of postmenopausal women experience hot flashes.

Keep track of your hot flashes, and if you experience 7 or more moderate to severe hot flashes a day due to menopause, consider talking to your doctor about PREMARIN.

Check out the Hot Flash Discussion Starter on www.PREMARIN.com to get started.

HOW COULD PREMARIN HELP?

PREMARIN has been shown to reduce the number of moderate to severe hot flashes due to menopause by over 80% at each dose studied* compared to 51% for placebo at 12 weeks.

Some women started to experience relief as soon as 4 weeks into treatment. But keep in mind that the amount of time it takes can be different for different women.

PREMARIN should be used at the lowest effective dose and for the shortest length of time consistent with your treatment goals and risks.

SELECTED SAFETY INFORMATION

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 out the cause.

Do not use estrogens with or without progestins to prevent heart disease, heart attacks, strokes or dementia (decline in brain function).

Using estrogen-alone may increase your chances of getting strokes or blood clots. Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.

Using estrogens, with or without progestins, may increase your chance of getting dementia, based on a study of women 65 years of age or older.

Estrogens should be used at the lowest dose possible, only for as long as needed. You and your healthcare provider should talk regularly about whether you still need treatment.

*Number of patients studied at each dose listed next to each dosage. 0.3 mg (n=30), 0.45 mg (n=32), 0.625 (n=27), placebo (n=28).

Please see Important Safety Information and Indication on page 1.

Please see accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.
YOU MAY BE ELIGIBLE TO SAVE ON PREMARIN (CONJUGATED ESTROGENS TABLETS, USP).*

Visit www.premarinsavings.com to activate your PREMARIN Savings Card today.

Eligible patients will pay a minimum of $15 with a savings of up to $55 per prescription fill. Limit 12 offers per calendar year. Maximum savings of $660 per calendar year. Terms and Conditions apply.

Visit www.PREMARIN.com for more information about PREMARIN.
For help with the PREMARIN Co-pay Card, call 1-866-410-3700.

*This card is not health insurance. This card is only accepted at participating pharmacies.

TERMS AND CONDITIONS

By participating in the PREMARIN® (conjugated estrogens tablets, USP) Co-pay Card program, you agree to the Terms and Conditions, you acknowledge that you currently meet the eligibility criteria and will comply with the Terms and Conditions described below:

- This coupon is not valid for prescriptions that are eligible to be reimbursed, in whole or in part, by Medicaid, Medicare, Tricare, or other federal or state healthcare programs (including any state prescription drug assistance programs) and the Government Health Insurance Plan available in Puerto Rico (formerly known as “La Reforma de Salud”).
- This coupon is limited to $55 or the amount of your co-pay, whichever is less.
- This coupon is not valid when the entire cost of your prescription drug is eligible to be reimbursed by your private insurance plans or other health or pharmacy benefit programs.
- This coupon is not valid where prohibited by law.
- This coupon cannot be combined with any other rebate/coupon, free trial, or similar offer for the specified prescription.
- You must deduct the savings received under this program from any reimbursement request submitted to your insurance plan, either directly by you or on your behalf.
- You must deduct the value of this coupon from any reimbursement request submitted to your insurance plan, either directly by you or on your behalf.
- Eligible patients will pay a minimum of $15 with a savings of up to $55 per prescription fill. Limit 12 offers per calendar year.
  - If your out-of-pocket cost is $70 or less, you will pay $15 and save up to $55.
  - If your out-of-pocket cost is more than $70, you will save $55 with this coupon and you must cover the remaining expenses.
- Maximum savings of $660 per calendar year. After you have reached the limit of $660, you will pay monthly out-of-pocket costs.
- This coupon cannot be combined with any other rebate/coupon, free trial, or similar offer for the specified prescription.
- This coupon will be accepted only at participating pharmacies.
- This coupon is not health insurance.
- This offer is good only in the U.S. and Puerto Rico.
- This coupon is limited to one per person during this offering period and is not transferable.
- Pfizer reserves the right to rescind, revoke, or amend this offer without notice at any time.
- This coupon and program expire on 1/31/2019.

For reimbursement when using a nonparticipating pharmacy/mail order: Pay for PREMARIN prescription and mail copy of original pharmacy receipt (cash register receipt NOT valid) with product name, date, and amount circled to: PREMARIN Co-pay Card, P.O. Box 4939, Warren, NJ 07059-6600. Be sure to include a copy of the front of your Co-pay Card, your name, and mailing address.

Visit www.PREMARIN.com for more information about PREMARIN. For help with the PREMARIN Co-pay Card, call 1-866-410-3700, or write: PREMARIN Co-pay Card, P.O. Box 4939, Warren, NJ 07059-6600. Be sure to include your name and mailing address.

Please see Important Safety Information and Indication on page 1.
Please see accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.
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, USP 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)

ADVERSE REACTIONS

Possible Serious Adverse Reactions With Estrogens

- 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, 5.11, 5.12)
- Monitor thyroid function in women on thyroid replacement therapy (5.13, 5.18)

Most common adverse reactions (≥ 5 percent) are: abdominal pain, asthenia, back pain, headache, flatulence, nausea, depression, insomnia, breast pain, endometrial hyperplasia, leukorrhea, 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

- Nursing Mothers: Estrogen administration has been shown to decrease the quantity and quality of breast milk (8.3)

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

Revised: 11/2017
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. Limitation 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 Prevention of Postmenopausal Osteoporosis. Limitation 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)

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Tablet Shape/Color</th>
<th>Imprint</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg</td>
<td>oval/green</td>
<td>PREMARIN 0.3</td>
</tr>
<tr>
<td>0.45 mg</td>
<td>oval/blue</td>
<td>PREMARIN 0.45</td>
</tr>
<tr>
<td>0.625 mg</td>
<td>oval/maroon</td>
<td>PREMARIN 0.625</td>
</tr>
<tr>
<td>0.9 mg</td>
<td>oval/white</td>
<td>PREMARIN 0.9</td>
</tr>
<tr>
<td>1.25 mg</td>
<td>oval/yellow</td>
<td>PREMARIN 1.25</td>
</tr>
</tbody>
</table>

4 CONTRAINDICATIONS

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

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer except in appropriately selected patients being treated for metastatic disease
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or a history of these conditions
- Active arterio-venous thromboembolic disease (for example stroke and MI), or a history of these conditions
- Known anaphylactic reaction or angioedema with Premarin
- Known liver impairment or disease
- Known protein C, protein S or antithrombin deficiency, or other known thrombophilic disorders.
- Known or suspected pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 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).

In the WHI estrogen plus progesterin 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. Should a stroke occur or be suspected, estrogen plus progesterin therapy should be discontinued immediately.

Coronary Heart Disease

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

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).

In the WHI estrogen plus progesterin 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). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 though 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 [see Clinical Studies (14.5)]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progesterin substudy, a statistically significant 2-fold greater risk of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (26 versus 15 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 [see Clinical Studies (14.5)]. Should a VTE occur or be suspected, estrogen plus progesterin therapy should be discontinued immediately.

It 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.
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 percent Caucasian), 1,012 women were treated with conjugated estrogens, and 1,321 were treated with placebo.

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

| Table 1: TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY ≥ 1 PERCENT |
| PREMARIN | PREMARIN | PREMARIN | Placebo |
| 0.625 mg (n=348) | 0.45 mg (n=338) | 0.3 mg (n=326) | (n=332) |
| **Body as a whole** | | | |
| Abdominal pain | 38 (11) | 26 (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 | 40 (12) | 47 (14) | 44 (13) | 46 (14) |
| Migraine | 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) | 1 (0) |
| Vasodilatation | 2 (1) | 2 (1) | 2 (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) | 6 (2) | 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) | 15 (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) | 4 (1) |
| **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 (5) | 10 (3) | 13 (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 | 10 (3) | 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) | 3 (1) | 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 neoplasms | 4 (1) | 4 (1) | 7 (2) | 7 (2) |
| Breast pain | 10 (3) | 29 (12) | 24 (7) | 28 (8) |
| Cervix disorder | 8 (2) | 4 (1) | 5 (2) | 2 (1) |
| 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 | 17 (5) | 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 metronidazole | 14 (4) | 10 (3) | 12 (4) | 5 (4) |
| 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; dysmenorrhea 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 menigioma.

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 conjugated estrogens and medroxyprogesterone acetate 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 conjugated estrogens.

7.1 Metabolic Interactions

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

8 USE IN SPECIFIC POPULATIONS

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

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

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]), 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)].

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 conjugated estrogens 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 equilenin sulfate. It contains concomitant components as sodium sulfate conjugates, 17α-dihydroequilenin, 17β estradiol, and 17β-dihydroequilenin. 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 conjugated estrogens. 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, cornstarch, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, powdered cellulose, sucrose, and titanium dioxide. Each tablet strength contains the following colors:

<table>
<thead>
<tr>
<th>Tablet strength</th>
<th>Tablet color contains</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg</td>
<td>D&amp;C Yellow No. 10 and FD&amp;C Blue No. 2</td>
</tr>
<tr>
<td>0.45 mg</td>
<td>FD&amp;C Blue No. 2</td>
</tr>
<tr>
<td>0.625 mg</td>
<td>FD&amp;C Blue No. 2 and FD&amp;C Red No. 40</td>
</tr>
<tr>
<td>0.9 mg</td>
<td>FD&amp;C Red No. 30 and D&amp;C Red No. 7</td>
</tr>
<tr>
<td>1.25 mg</td>
<td>Black iron oxide, D&amp;C Yellow No. 10 and FD&amp;C Yellow No. 6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Tablet strength</th>
<th>Dissolution Test criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMARIN 1.25 mg tablets</td>
<td>USP Dissolution Test 4</td>
</tr>
<tr>
<td>PREMARIN 0.3 mg, 0.45 mg and 0.625 mg tablets</td>
<td>USP Dissolution Test 5</td>
</tr>
<tr>
<td>PREMARIN 0.9 mg tablets</td>
<td>USP Dissolution Test 6</td>
</tr>
</tbody>
</table>

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 estrogen receptor level.

12.2 Pharmacodynamics

There are no pharmacodynamic data for PREMARIN.

12.3 Pharmacokinetics

Conjugated estrogens are water-soluble and are absorbed from the gastrointestinal tract after release from the drug formulation. The PREMARIN tablet releases conjugated estrogens slowly over several hours. Table 2 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens 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 Cmax and AUC of estrogens were altered approximately 3-15%. The changes to Cmax and AUC are not considered clinically meaningful, therefore PREMARIN may be taken without regard to meals.

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 [see Warnings and Precautions (5.3), and Clinical Studies (14.6)].
14 CLINICAL STUDIES
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13 NONCLINICAL TOXICOLOGY

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 conjugated estrogens, with or without medroxyprogesterone acetate. 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.

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. (conjugated estrogens alone and conjugated estrogens/medroxyprogesterone acetate 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 (L2 to L4). Secondary, 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 (L2 to L4 BMD) at the final on-therapy evaluation (cycle 26 for those who completed treatment) 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, or 0.3 mg, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L2 to L4). Secondary, 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

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The mean percent changes from baseline in L2 to L4 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 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 L2 to L4 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 (ΔBA/ΔCA) 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-progesterin 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, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

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

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 percent CI 0.36-1.09)] and overall mortality [HR 0.71 (95 percent CI 0.46-1.11)].

WHI Estrogen Plus Progestin Substudy

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

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

Results of the estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79, 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 6. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

### TABLE 5: RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN ALONE SUBSTUDY OF WHI

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE vs. Placebo (95% CI)</th>
<th>Placebo n = 5,429</th>
<th>Absolute Risk per 10,000 Women-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>0.95 (0.78–1.16)</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>2.91 (0.73–1.14)</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.01 (0.71–1.43)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>All Stroke</td>
<td>1.33 (1.05–1.68)</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.55 (1.19–2.01)</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.47 (1.06–2.06)</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.37 (0.90–2.07)</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>0.80 (0.62–1.04)</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.08 (0.75–1.55)</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.65 (0.45–0.94)</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>0.64 (0.44–0.93)</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Lower arm/wrist fractures</td>
<td>0.58 (0.47–0.72)</td>
<td>35</td>
<td>59</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.71 (0.64–0.80)</td>
<td>144</td>
<td>197</td>
</tr>
<tr>
<td>Death due to other causes</td>
<td>1.08 (0.88–1.32)</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>1.04 (0.88–1.22)</td>
<td>79</td>
<td>75</td>
</tr>
</tbody>
</table>

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

1. Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
2. Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
3. Results are based on an average follow-up of 6.8 years.
4. All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.
5. 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.
6. Not included in “global index.”
7. Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
8. Nonsignificant.
9. All-cause mortality.
10. Subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo.
11. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined.
12. Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile.
13. 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 percent CI 0.36-1.09)] and overall mortality [HR 0.71 (95 percent CI 0.46-1.11)].
The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy women 50-59 years of age, a non-significant trend toward reduced risk for overall mortality (HR 0.69 (95 percent CI 0.44-1.07)).

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall relative risk for probable dementia was 1.76 (95 percent CI 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women 65 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older).

The WHIMS estrogen plus progestin ancillary study enrolled 4,532 predominantly healthy postmenopausal women 65 to 79 years of age (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo 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.

Some findings are shown in Table 6:

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th>CE/MPA vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>1.23</td>
<td>(95 percent CI 0.99-1.53)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.28</td>
<td>(1.00-1.63)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.10</td>
<td>(0.70-1.75)</td>
</tr>
<tr>
<td>All strokes</td>
<td>1.31</td>
<td>(1.03-1.68)</td>
</tr>
<tr>
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<td>(1.09-1.90)</td>
</tr>
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<td>Deep vein thrombosis</td>
<td>1.95</td>
<td>(1.43-2.67)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.13</td>
<td>(1.45-3.11)</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.24</td>
<td>(1.01-1.54)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.61</td>
<td>(0.42-0.87)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.81</td>
<td>(0.48-1.36)</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1.44</td>
<td>(0.47-4.22)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.67</td>
<td>(0.47-0.96)</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>0.65</td>
<td>(0.46-0.92)</td>
</tr>
<tr>
<td>Lower arm/wrist fractures</td>
<td>0.71</td>
<td>(0.59-0.85)</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.76</td>
<td>(0.69-0.83)</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>1.00</td>
<td>(0.83-1.19)</td>
</tr>
<tr>
<td>Global Index</td>
<td>1.13</td>
<td>(1.02-1.25)</td>
</tr>
</tbody>
</table>


15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PREMARIN® (conjugated estrogens tablets, USP) — Each oval blue tablet contains 0.45 mg, in bottles of 100 (NDC 0046-1101-91) and 1,000 (NDC 0046-1101-91).

— Each oval green tablet contains 0.3 mg, in bottles of 100 (NDC 0046-1101-81) and 1,000 (NDC 0046-1101-81).

— Each oval white tablet contains 0.9 mg, in bottles of 100 (NDC 0046-1103-81) and 1,000 (NDC 0046-1104-81).

— Each oval yellow tablet contains 1.25 mg, in bottles of 100 (NDC 0046-1104-81) and 1,000 (NDC 0046-1104-91).

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

See 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.

Distributed by

Pfizer

Wyeth Pharmaceuticals Inc

A subsidiary of Pfizer Inc, Philadelphia, PA 19101

LAB-0467-6.0
PATIENT INFORMATION
PREMARIN® (prem-uh-rin)
(Conjugated estrogen tablets, USP)

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 flashes
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 flashes” or “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.
• Think you may be pregnant
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 breastfeeding
The hormones in PREMARIN can pass into your 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
• Dementia
• Breast cancer
• Cancer of the lining of the uterus (womb)
• Cancer of the ovary
• High blood pressure
• High blood sugar
• Gallbladder disease
• Liver problems
• Enlargement of benign tumors of the uterus (“fibroids”)
• Severe allergic reactions

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:
• New breast lumps
• Unusual vaginal bleeding
• Changes in vision or speech
• Sudden new severe headaches
• Severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
• Swollen lips, tongue and face

Less serious, but common side effects 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, 17α-dihydroequilin, 17α-estradiol, and 17β-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.

These 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 label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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