Doctor Discussion Guide

What to tell your doctor, what to ask, and how to start the conversation in the first place when intercourse is painful after menopause.

How to start the conversation

There are many ways to do this. What matters most is that you feel comfortable and that you communicate your needs to your doctor. Here are a few approaches:

- The direct approach: “Since menopause, intercourse has been painful. What can I do?”
- The unwelcome surprise: “You know, I expected hot flashes and night sweats. I never expected pain during intimacy. What can I do?”
- The show-me: “There’s something else that’s been bothering me. I’d like you to take a look at this” (then hand your doctor this guide).

Things to ask your doctor

- Will my vaginal symptoms go away on their own?
- How effective could vaginal estrogen treatments be for my situation?
  - What are the possible side effects?
  - How are the treatments used?
  - How long would I need to use it?
- Can over-the-counter treatments solve my problem?

Things to tell your doctor

- All medications you’re currently taking
- Your medical history, including current or past health problems
- How long it’s been since your last period
- Any menopausal vaginal symptoms you’re experiencing, such as itching, burning, dryness, or painful intercourse
- How vaginal symptoms impact your relationships and your sexual life

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 (conjugated estrogens) Vaginal Cream. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

Do not use 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 (conjugated estrogens) Vaginal Cream 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.

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.

Common side effects include headache, pelvic pain, breast pain, vaginal bleeding and vaginitis.

INDICATION

Premarin (conjugated estrogens) Vaginal Cream is used after menopause to treat menopausal changes in and around the vagina and to treat moderate to severe painful intercourse caused by these changes.

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

PREMARIN (conjugated estrogens) Vaginal Cream.
Initial U.S. Approval: 1946

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA
See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy
• There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)
• Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
• The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)
• The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

Estrogen Plus Progestin Therapy
• Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
• The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) (5.2)
• The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)
• The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

CONTRAINDICATIONS
• Known or suspected estrogen-dependent neoplasia (4, 5.3)
• Known, suspected, or history of breast cancer (4, 5.3)
• Undiagnosed abnormal genital bleeding (4)

DOSE AND ADMINISTRATION
• Cyclic administration of 0.5 to 2 g intra-vaginally [daily for 21 days then off for 7 days] for Treatment of Atrophic Vaginitis and Kraurosis Vulvae (2.1)
• Cyclic administration of 0.5 g intra-vaginally [daily for 21 days then off for 7 days] for Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause (2.2)

DOSE FORMS AND STRENGTHS
• Each gram contains 0.625 mg conjugated estrogens, USP (3)
• Each applicator(s) calibrated in 0.5 g increments to a maximum of 2 g, or a net wt. 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5 g increments to a maximum of 2 g (3)

ADVERSE REACTIONS
In a prospective, randomized, placebo-controlled, double-blind study, the most common adverse reactions > 2 percent are headache, pelvic pain, vasodilation, breast pain, leucorrhea, metrorrhagia, vaginitis, vulvovaginal disorder (6.1)

USING IN SPECIFIC POPULATIONS
• Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
• Genitourinary: An increased risk of probable dementia in women over 65 years of age was reported in the Women’s Health Initiative Memory ancillary studies of the Women’s Health Initiative (5.4, 8.5)

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

REVISED: 05/2012

FULL PRESCRIBING INFORMATION: CONTENTS*
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WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA

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 should follow any directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal vaginal bleeding (see Warnings and Precautions (3.2)).

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disorders or dementia (see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)).

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 (5.4), and Clinical Studies (14.2)).

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)).

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogen plus progestin therapy should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Breast Cancer

Estrogens plus progestin therapy should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

PREMARIN Vaginal Cream Therapy should not be used in women with any of the following conditions:

- Un diag nosed ab nal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
- Active anaphylactic reaction or angioedema to PREMARIN Vaginal Cream
- Known liver dysfunction or disease
- Known protein C, protein S or antithrombin deficiency or other known thrombophilic disorders
- Known or suspected pregnancy

5.2 Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted (see Clinical Studies (14.2)). Should a stroke occur or be suspected, estrogen plus progestin 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 16 per 10,000 women-years). In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone plus MPA (2.5 mg) compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years) (see Clinical Studies (14.2)). The increase in risk was demonstrated in year 2 and persisted (see Clinical Studies (14.2)). Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo (see Clinical Studies (14.2)).

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)-alone plus medroxyprogesterone acetate (MPA) (2.5 mg), relative to placebo (see Warnings and Precautions (5.2), and Clinical Studies (14.2)).

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events (CE (0.625 mg)-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years). In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).

An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 (see Clinical Studies (14.2)).

In postmenopausal women with documented coronary 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)-alone plus MPA (2.5 mg) demonstrated a non-significant 2-fold greater risk of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during subsequent years. Two thousand, three hundred and twenty-one (3,321) 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 plus MPA 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 (20 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 (14.2)). Should a VTE occur or be suspected, estrogen therapy should be discontinued immediately.

In the WHI estrogen plus progestin 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 (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 9 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted (see Clinical Studies (14.2)). Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

5.3 Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among estrogen-alone users was reported to be 2.5 times greater than in non-users, and appears dependent on duration of therapy and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk is with use for more than 10 years, but in users of estrogen for less than 5 years, the risk is not increased.
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 genital bleeding.

There is no evidence that estrogen has a role in a different endometrial risk profile than synthetic profiles of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which is related to estrogen therapy. In a 52-week clinical trial using PREMARIN Vaginal Cream alone (0.5% inserted twice weekly or daily for 21 days, then off for 7 days), there was no evidence of endometrial hyperplasia or endometrial carcinoma.

5.4 Probable Dementia

In the WHI 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 1.52 (95 percent CI, 0.77-3.0). The absolute risk for CE-alone versus placebo was 2% versus 1% cases per 10,000 women-years. In some randomized controlled trials and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone concentrations may occur in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

5.16 Anaphylactic Reactions and Angioedema

The administration of estrogen plus progestin results in a small number of cases of hours to days after orally administered PREMARIN and require emergency management, have been reported in the postmarketing setting. Skin (hives, pruritus, swelling (lip-and-tongue) and either respiratory tract (inhalation) or gastrointestinal tract (vomiting, diarrhea) involvement has been noted. Angioedema involving the tongue, larynx, face, and feet requiring medical intervention has occurred. Clinical symptoms were usually observed in the first several days after starting or increasing the dose of oral estrogen plus progestin therapy. 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 oral PREMARIN should not receive oral PREMARIN again.

5.17 Hereditary Angiodyplasia

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

5.18 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatitis hemangiomata and should be used with caution in women with these conditions.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical experience of a different drug or drug regimen. In the clinical trials of this drug, reactions in 22% of the patients treated with placebo were observed in 18% of the patients treated with oral estrogens.
Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Reactions ≥1

<table>
<thead>
<tr>
<th>Body System</th>
<th>Treatment</th>
<th>Placebo 2x/wk N=68</th>
<th>Placebo 2x/wk N=140</th>
<th>Placebo 21/7 N=72</th>
<th>PVC 21/7 N=143</th>
</tr>
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<tbody>
<tr>
<td>Only</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Abdominal</td>
<td>(1.5)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>(1.5)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>(1.5)</td>
<td>2 (1.4)</td>
<td>2 (1.4)</td>
<td>(1.5)</td>
<td></td>
</tr>
<tr>
<td>Mammillia</td>
<td>(1.5)</td>
<td>0</td>
<td>1 (1.4)</td>
<td>(0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pelvic Pain</td>
<td>(1.5)</td>
<td>4 (2.8)</td>
<td>2 (2.8)</td>
<td>(2.9)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
<td>(1.5)</td>
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<tr>
<td>Nervous System</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>(1.5)</td>
<td>0</td>
<td>0</td>
<td>1 (1.5)</td>
<td></td>
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<tr>
<td>Skin and Appendages</td>
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<td></td>
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<tr>
<td>Acne</td>
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<td>2 (1.4)</td>
<td>0</td>
<td>0</td>
<td>(1.5)</td>
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<tr>
<td>Erythema</td>
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<td>0</td>
<td>0</td>
<td>(1.5)</td>
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<tr>
<td>Pruritus</td>
<td>2 (1.4)</td>
<td>0</td>
<td>1 (1.4)</td>
<td>(0.7)</td>
<td>0</td>
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<tr>
<td>Unorganized System</td>
<td></td>
<td></td>
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<tr>
<td>Breast Enlargement</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Breast Pain</td>
<td>7 (4.9)</td>
<td>0</td>
<td>3 (2.1)</td>
<td>0</td>
<td>(2.9)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>2 (1.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Leukorrhea</td>
<td>3 (2.1)</td>
<td>1 (1.4)</td>
<td>4 (2.9)</td>
<td>0</td>
<td>(2.9)</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Urinary Frequency</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
<td>(1.5)</td>
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<tr>
<td>Urinary Urgency</td>
<td>1 (1.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>(1.5)</td>
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<tr>
<td>Vaginal Frencourage</td>
<td>2 (1.4)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Vaginal Malocinna</td>
<td>2 (1.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>2 (1.4)</td>
<td>0</td>
<td>3 (2.1)</td>
<td>3 (4.4)</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Vulvovaginal Disorder</td>
<td>4 (2.8)</td>
<td>0</td>
<td>3 (2.1)</td>
<td>2 (2.9)</td>
<td></td>
</tr>
</tbody>
</table>

* Body system totals are not necessarily the sum of individual adverse events, since a patient may report two or more different adverse reactions in the same body system.

8.4 Pediatric Use
PREMARIN Vaginal Cream is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use
There have been insufficient numbers of geriatric women involved in clinical studies utilizing PREMARIN Vaginal Cream to determine whether those over 65 years of age differ from younger subjects in their response to PREMARIN Vaginal Cream.

The Women's Health Initiative Studies
In the WHI estrogen-alone substudy (daily 0.625 mg-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age (see Warnings and Precautions (5.2), Clinical Studies (14.2)).

In the WHI estrogen plus progestin substudy (daily 0.625 mg plus MPA 2.5 mg-alone versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age (see Warnings and Precautions (5.2, 5.3), Clinical Studies (14.2)).

The Women's Health Initiative Memory Study
In the WHIMS ancillary studies 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 (5.4), and Clinical Studies (14.3)).

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women (see Warnings and Precautions (5.4), and Clinical Studies (14.3)).

8.8 Pregnancy
The effect of renal impairment on the pharmacokinetics of PREMARIN Vaginal Cream has not been studied.

8.7 Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of PREMARIN Vaginal Cream has not been studied.

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

1. DESCRIPTION
Each gram of PREMARIN (conjugated estrogens) Vaginal Cream contains 0.625 mg conjugated estrogens, USP, in a nonoily, nonirritating base containing cetyl esters wax, cetyl alcohol, white beeswax, glycerol monostearate, propylene glycol monostearate, methyl stearate, bencil alcohol, sodium lauryl sulfate, glycine, and mineral oil. PREMARIN Vaginal Cream is applied intravaginally.

PREMARIN Vaginal Cream contains a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of estrogen sulfone estrogens. The sulfones represent the average composition of material derived from pregnant mare's urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, sodium sulfate, cetyl alcohol, 17-α-ethinylestradiol, 17-α-estradiol, and 17 β-estradiol.

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

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, which is secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfated-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

12.2 Pharmacodynamics
Currently, there are no pharmacodynamic data known for PREMARIN Vaginal Cream.

12.3 Pharmacokinetics
Absorption
Conjugated estrogens are water soluble and are well-absorbed through the skin, mucous membranes, and the gastrointestinal (GI) tract. The vaginal delivery of estrogens circumvents first-pass metabolism.

A bioavailability study was conducted in 24 postmenopausal women with atrophic vaginitis. The mean (SD) pharmacokinetic parameters for unconjugated estrone, unconjugated estradiol, total estrone, total estradiol and total equilin following 7 once-daily doses of PREMARIN Vaginal Cream 0.5 g is shown in Table 2.

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

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Arithmetic Mean ± SD</th>
<th>Cmax (pg/mL)</th>
<th>Tmax (hr)</th>
<th>AUC (ng/hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrone</td>
<td>42.0 ± 13.9</td>
<td>7.4 ± 6.2</td>
<td>826 ± 295</td>
<td></td>
</tr>
<tr>
<td>Estrone-17α-estradiol</td>
<td>21.9 ± 13.1</td>
<td>7.4 ± 6.7</td>
<td>316 ± 250</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>12.8 ± 16.6</td>
<td>8.5 ± 6.2</td>
<td>231 ± 285</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>9.14 ± 14.7</td>
<td>8.5 ± 6.2</td>
<td>161 ± 252</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Arithmetic Mean ± SD</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (hr)</th>
<th>AUC (ng/hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrone</td>
<td>0.40 ± 0.37</td>
<td>6.6 ± 4.00</td>
<td>9.3 ± 4.69</td>
<td></td>
</tr>
<tr>
<td>Estrone-17α-estradiol</td>
<td>0.40 ± 0.28</td>
<td>6.6 ± 4.00</td>
<td>5.79 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.04 ± 0.04</td>
<td>7.7 ± 5.9</td>
<td>0.70 ± 0.42</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.04 ± 0.04</td>
<td>7.7 ± 5.9</td>
<td>0.49 ± 0.38</td>
<td></td>
</tr>
<tr>
<td>Total equilin</td>
<td>0.12 ± 0.15</td>
<td>6.1 ± 4.7</td>
<td>3.09 ± 1.37</td>
<td></td>
</tr>
</tbody>
</table>
Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exhibit a dynamic equilibrium of metabolic interconversions. These transformations take place only in the liver. Estrogens are converted reversibly to estrone, and both can be converted to estradiol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfation and glucuronide conjugation in the liver. Biliary secretion of conjugates into the intestine and their hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a storage reservoir for the formation of more active estrogens.

**13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

**14 CLINICAL STUDIES**

14.1 Effects on Vulvar and Vaginal Atrophy

A 12-week, prospective, randomized, double-blind placebo-controlled study was conducted to compare the safety and efficacy of 2 PREMARIN Vaginal Cream (PVC) regimens (0.5 g (0.3 mg CE) administered twice weekly and 0.5 g (0.3 mg CE) administered sequentially for 21 days on drug followed by 7 days off to matching placebo regimens in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. The initial 12-week, double-blind, placebo-controlled phase was followed by an open-label phase to assess endometrial safety through week 52. The study randomized 422 generally healthy postmenopausal women between 44 to 77 years of age (mean 57.8 years), who at baseline had ≤5 percent superficial cells on a vaginal smear, a vaginal pH ≤5.5, and who identified a most bothersome moderate to severe symptom of vulvar and vaginal atrophy. The majority (92.2 percent) of the women were Caucasian (n = 390); 7.8 percent were Other (n = 32). All subjects were assessed for improvement in the mean change from baseline to Week 12 for the co-primary efficacy variables of: most bothersome symptom of vulvar and vaginal atrophy due to menopause; and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints.

---

### Table 3: Mean Change in Dyspareunia Severity Compared to Placebo MTP Population of Most Bothersome Symptom Score for Dyspareunia, LOCa

<table>
<thead>
<tr>
<th>Dyspareunia</th>
<th>PVC 0.5 g 2/week</th>
<th>Placebo 0.5 g 2/week</th>
<th>PVC 0.5 g 21/7</th>
<th>Placebo 0.5 g 21/7</th>
<th>PVC 0.5 g 2/week</th>
<th>Placebo 0.5 g 21/7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>2.42 (0.76)</td>
<td>2.28 (1.04)</td>
<td>2.26 (0.99)</td>
<td>2.32 (0.88)</td>
<td>2.22 (1.04)</td>
<td>2.32 (0.88)</td>
</tr>
</tbody>
</table>

Baseline

<table>
<thead>
<tr>
<th>Week 12</th>
<th>0.22 (0.96)</th>
<th>1.63 (1.16)</th>
<th>0.77 (1.05)</th>
<th>1.19 (1.03)</th>
<th>1.95 (1.23)</th>
<th>1.48 (1.17)</th>
</tr>
</thead>
</table>

Change from Baseline at Week 12

<table>
<thead>
<tr>
<th>PVC 2/week</th>
<th>PVC 21/7</th>
<th>Placebo 2/week</th>
<th>Placebo 21/7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.01</td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

P-value vs. Placebo

<table>
<thead>
<tr>
<th>PVC 2/week</th>
<th>PVC 21/7</th>
<th>Placebo 2/week</th>
<th>Placebo 21/7</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.01</td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHIc,d

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th>CE vs. Placebo (95% nCI)</th>
<th>CE n = 5,310</th>
<th>Placebo n = 5,429</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events\a</td>
<td>0.95 (0.78–1.16)</td>
<td>54</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI\a</td>
<td>0.92 (0.73–1.14)</td>
<td>40</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>CHD death\a</td>
<td>2.01 (0.71–4.13)</td>
<td>16</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>All Stroke\ab</td>
<td>1.33 (1.05–1.68)</td>
<td>45</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke\ab</td>
<td>1.55 (1.19–2.01)</td>
<td>38</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis\ab</td>
<td>1.79 (1.30–2.46)</td>
<td>43</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism\ab</td>
<td>1.37 (0.90–2.07)</td>
<td>14</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Invasive breast cancer\ab</td>
<td>0.80 (0.62–1.04)</td>
<td>28</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer\ab</td>
<td>1.08 (0.75–1.55)</td>
<td>17</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Lower arm/wrist fractures\bc</td>
<td>0.65 (0.45–0.94)</td>
<td>12</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Vertebral fractures\bc</td>
<td>0.64 (0.44–0.93)</td>
<td>11</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Lower arm/wrist fractures\b</td>
<td>0.58 (0.47–0.72)</td>
<td>35</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Total fractures\b</td>
<td>0.71 (0.64–0.80)</td>
<td>144</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>Death due to other causes\b,c</td>
<td>1.08 (0.86–1.32)</td>
<td>53</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Overall mortality\b,c</td>
<td>1.04 (0.88–1.22)</td>
<td>79</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

Global Index\b,c | 1.02 (0.92–1.13) | 206 | 201 |

- Adapted from numerous WHI publications. WHI publications can be viewed at whi.osf.org.
- Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
- Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
- Results are based on an average follow-up of 6.8 years.
- Not included in "global index."
Table 5: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years (Cont.)

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE/MPA vs. Placebo (95% CI)</th>
<th>CE/MPA Placebo</th>
<th>Placebo</th>
<th>Absolute Risk per 10,000 Women-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive breast cancer*</td>
<td>1.24 (1.01–1.54)</td>
<td>8.506</td>
<td>8.102</td>
<td>41</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.61 (0.42–0.87)</td>
<td>10</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Endometrial cancer*</td>
<td>0.81 (0.48–1.36)</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1.94 (0.74–4.92)</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.67 (0.47–0.96)</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Vertebral fractures*</td>
<td>0.85 (0.46–0.92)</td>
<td>11</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Lower arm/riest fractures*</td>
<td>0.71 (0.59–0.85)</td>
<td>44</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Total fractures*</td>
<td>0.76 (0.69–0.83)</td>
<td>152</td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>Overall Mortality*</td>
<td>1.00 (0.83–1.19)</td>
<td>52</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Global index*</td>
<td>1.13 (1.02–1.25)</td>
<td>184</td>
<td>165</td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
* Results are based on centrally adjudicated data.
* Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
* Not included in “global index.”
* Includes metastatic and non-metastatic breast cancer, with the exception of in situ cancer.
* All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
* A subset of the events combined in a “global index” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age, a non-significant trend toward reduced risk for overall mortality (HR 0.89 (95 percent CI, 0.84-1.07)).

14.3 Women’s Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age. Women 65 to 79 years of age were randomized to the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)].

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo. After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer’s disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)].

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo. After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)].

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women [see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)].

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PREMARIN (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

Combination package: Each contains a net wt of 1.06 oz (30 g) tube with plastic applicator(s) calibrated in 0.5 g increments to a maximum of 2 g (NDC 0046-0872-21), or a net wt 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5 g increments to a maximum of 2 g (NDC 0046-0872-93).

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].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

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 (5.3)].

17.2 Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia [see Warnings and Precautions (5.2, 5.3, 5.4)].

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

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

17.4 Instructions for Use of Applicator

Step 1. Remove cap from tube.
Step 2. Squeeze nozzle end of applicator onto tube (Figure A).
Step 3. Gently squeeze tube from the bottom to force sufficient cream into the barrel to provide the prescribed dose. Use the marked stopping points on the applicator to measure the correct dose, as prescribed by your healthcare provider (Figure B).
Step 4. Unscrew applicator from tube.
Step 5. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position (Figure C).
Step 6. TO CLEANSE: Pull plunger to remove it from barrel. Wash with mild soap and warm water (Figure D). DO NOT BOIL OR USE HOT WATER.
FDA-Approved Patient Labeling
PREMARIN® (conjugated estrogens) Vaginal Cream
Read this PATIENT INFORMATION before you start using PREMARIN Vaginal Cream and read what you get each time you refill your PREMARIN Vaginal Cream prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about PREMARIN Vaginal Cream (an estrogen mixture)?

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb). Report any unusual vaginal bleeding right away while you are using PREMARIN Vaginal Cream. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline in brain function).
- Using estrogen-alone may increase your chances of getting strokes or blood clots.
- 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 Vaginal Cream.

What is PREMARIN Vaginal Cream?
PREMARIN Vaginal Cream is a medicine that contains a mixture of estrogen hormones. It is used after menopause to:

- Treat menopausal changes in and around the vagina.
- Treat painful intercourse caused by menopausal changes of the vagina.

Who should not use PREMARIN Vaginal Cream?
Do not start using PREMARIN Vaginal Cream if you:

- Have unusual vaginal bleeding.
- Currently have or have had certain cancers. Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use PREMARIN Vaginal Cream.
- Had a stroke or heart attack.
- Currently have or have had blood clots.
- Currently have or have had liver problems.
- Have been diagnosed with a bleeding disorder.
- Are allergic to PREMARIN Vaginal Cream or any of its ingredients.

Tell your healthcare provider:

- If you have unusual vaginal bleeding. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- About all your medical problems.
- If you are going to have surgery or will be on bedrest.
- About the medicines you take.

This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PREMARIN Vaginal Cream works. PREMARIN Vaginal Cream may also affect how your other medicines work.

- If you are pregnant.
- If you are breast feeding.
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you.

How should I use PREMARIN Vaginal Cream?
PREMARIN Vaginal Cream is a cream that you place in your vagina with the applicator provided with the cream.

Step 1. Remove cap from tube.
Step 2. Screw nozzle end of applicator onto tube (Figure A).
Step 3. Gently squeeze tube from the bottom to force sufficient cream into the barrel to provide the prescribed dose. Use the marked stopping points on the applicator to measure the correct dose, as prescribed by your healthcare provider (Figure B).
Step 4. Unscrew applicator from tube.
Step 5. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position (Figure C).
Step 6. TO CLEANSE: Pull plunger to remove it from barrel. Wash with mild soap and warm water (Figure D).

DO NOT BOIL OR USE HOT WATER.

What is the most important information I should know about PREMARIN Vaginal Cream (an estrogen mixture)?

- **Serious, but less common side effects include:**
  - Heart attack
  - Stroke
  - Blood clots
  - Dementia
  - Breast cancer
  - Cancer of the lining of the uterus (womb)
  - Cancer of the ovary
  - High blood pressure
  - High blood sugar
  - Gallbladder disease
  - Liver problems
  - Enlargement of benign tumors of the uterus ("fibroids")
  - Severe allergic reaction

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- New breast lumps
- Unusual vaginal bleeding
- Changes in vision or speech
- Sudden new severe headaches
- Severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- Swollen lips, tongue or face

Less serious, but common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach or abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection
- Reactions from inserting PREMARIN Vaginal Cream, such as vaginal burning, irritation, and itching

These are not all the possible side effects of PREMARIN Vaginal Cream. For more information, ask your healthcare provider or pharmacist for advice about side effects. You may report side effects to Pfizer Inc. at 1-800-438-1985 or to FDA at 1-800-FDA-1088.

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

- Talk with your healthcare provider regularly about whether you should continue using PREMARIN Vaginal Cream.

- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you.
The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus. See your healthcare provider right away if you get vaginal bleeding while using PREMARIN Vaginal Cream.

- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else.
- If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease.

Ask your healthcare provider for ways to lower your chances for getting heart disease.

**General information about the safe and effective use of PREMARIN Vaginal Cream**

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

Keep PREMARIN Vaginal Cream out of the reach of children.

Latex or rubber condoms, diaphragms and cervical caps may be weakened and fail when they come into contact with PREMARIN Vaginal Cream.

This leaflet provides a summary of the most important information about PREMARIN Vaginal Cream. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about PREMARIN Vaginal Cream that is written for health professionals.

**What are the ingredients in PREMARIN Vaginal Cream?**

PREMARIN Vaginal Cream contains a mixture of conjugated estrogens, which are a mixture of sodium estrone sulfate and sodium equilenin sulfate and other components, including sodium sulfate conjugates: 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin. PREMARIN Vaginal Cream also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl mono- and di-stearate, propylene glycol, propylene glycol mono- and disterate, methyl stearate, sodium lauryl sulfate, glycerin, and mineral oil.

PREMARIN (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

Combination package: Each contains a net wt. of 1.06 oz (30 g) tube with plastic applicator(s) calibrated in 0.5 g increments to a maximum of 2 g (NDC 0046-0872-21), or a net wt. 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5 g increments to a maximum of 2 g (NDC 0046-0872-93).

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

This product’s label may have been updated. For current full prescribing information, please visit www.pfizer.com

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