

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**20216Orig1s043**

*Trade Name:* **Premarin**  
*Generic or Proper Name:* conjugated estrogens  
*Sponsor:* WYETH PHARMACEUTICALS LLC  
*Approval Date:* December 4, 1998  
*Indication:* **Premarin** (conjugated estrogens) Vaginal Cream is a mixture of estrogens indicated for:

- Treatment of Atrophic Vaginitis and Kraurosis Vulvae
- Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to menopause.

# CENTER FOR DRUG EVALUATION AND RESEARCH

20216Orig1s043

## CONTENTS

### Reviews / Information Included in this NDA Review.

|  |          |
|--|----------|
| <b>Approval Letter</b>                               | <b>X</b> |
| <b>Other Action Letters</b>                          |          |
| <b>Labeling</b>                                      | <b>X</b> |
| <b>REMS</b>  |          |
| <b>Summary Review</b>                                |          |
| <b>Officer/Employee List</b>                         |          |
| <b>Division Director Review</b>                      |          |
| <b>Cross Discipline Team Leader Review</b>           |          |
| <b>Clinical Review(s)</b>                            |          |
| <b>Product Quality Review(s)</b>                     | <b>X</b> |
| <b>Non-Clinical Review(s)</b>                        |          |
| <b>Statistical Review(s)</b>                         |          |
| <b>Clinical Microbiology / Virology Review(s)</b>    |          |
| <b>Clinical Pharmacology Review(s)</b>               |          |
| <b>Other Reviews</b>                                 |          |
| <b>Risk Assessment and Risk Mitigation Review(s)</b> |          |
| <b>Proprietary Name Review(s)</b>                    |          |
| <b>Administrative/Correspondence Document(s)</b>     | <b>X</b> |

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20216Orig1s043**

**APPROVAL LETTER**

NDA 20-216/S-043

DEC 04 1998

Wyeth-Ayerst Laboratories  
Attention: Joseph S. Sonk, Ph.D.  
Senior Director, U.S. Drug Regulatory Affairs  
Box 8299  
Philadelphia, PA 19101-8299

Dear Dr. Sonk:

Please refer to your supplemental new drug application dated June 4, 1998, received June 5, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin<sup>®</sup>, conjugated estrogens, USP, Vaginal Cream.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides for an

(b) (4)

(b) (4)

(b) (4) Your submission stated July 31, 1998, as the implementation date for the change.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Diane Moore, Project Manager, at (301) 827-4260.

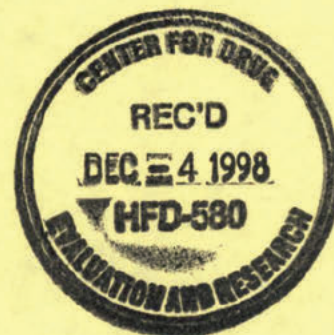
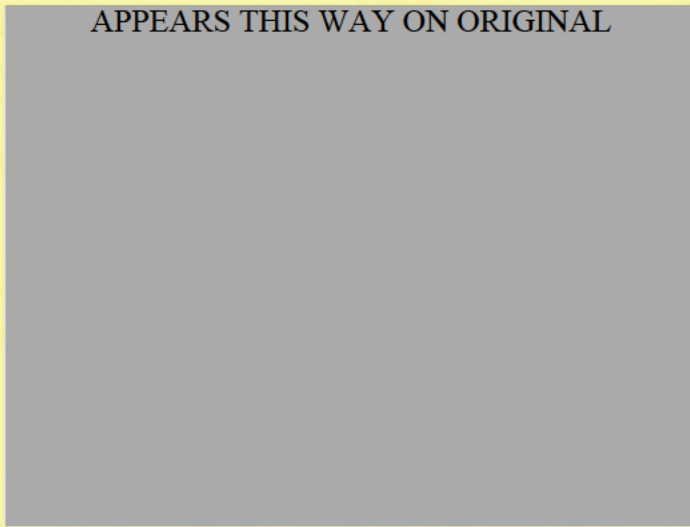
Sincerely,

*Moo-Jhong Rhee* 12/4/98

Moo-Jhong Rhee, Ph.D.  
Chemistry Team Leader for  
Division of Reproductive and Urologic Drug  
Products (HFD-580)  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research



APPEARS THIS WAY ON ORIGINAL



NDA 20-216/S-043

Page 2

cc:

Archival NDA 20-216

HFD-580/Div. Files

HFD-580/D.Moore

HFD-580/LRarick/MMann/SSlaughter/MRhee/DLin

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: dm/December 2, 1998

Concurrence:

TRumble 12.02.98/DLin, MRhee 12.03.98

filename: N20216S0.DOC

APPROVAL (AP)

*Diane Moore 12/4/98*

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

20216Orig1s043

**LABELING**

NDA 20-216/S-052

---

**NOTE: PATIENT INFORMATION LEAFLET ATTACHED.**

**Premarin<sup>®</sup>** (conjugated estrogens)  
**Vaginal Cream** in a nonliquefying base

**Rx only**

**ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER**

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of “natural” estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

**CARDIOVASCULAR AND OTHER RISKS**

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease.

The Women’s Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

The Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

**DESCRIPTION**

Each gram of Premarin<sup>®</sup> (conjugated estrogens) Vaginal Cream contains 0.625 mg conjugated estrogens, USP in a nonliquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. Premarin Vaginal Cream is applied intravaginally.

NDA 20-216/S-052

Page 4

Premarin (conjugated estrogens) Vaginal Cream is a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains estrone, equilin, and 17  $\alpha$ -dihydroequilin, together with smaller amounts of 17  $\alpha$ -estradiol, equilenin, and 17  $\alpha$ -dihydroequilenin as salts of their sulfate esters.

## **CLINICAL PHARMACOLOGY**

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

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogen 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 follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

## **Pharmacokinetics**

### ***Absorption***

Conjugated estrogens are soluble in water and are well absorbed through the skin, mucous membranes, and the gastrointestinal tract after release from the drug formulation.

### ***Distribution***

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentration in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone-binding globulin (SHBG) and albumin.

### ***Metabolism***

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant proportion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

NDA 20-216/S-052

Page 5

### ***Excretion***

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

### **Special Populations**

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

### **Drug Interactions**

Data from a single-dose drug-drug interaction study involving oral conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic dispositions of both drugs are not altered when the drugs are coadministered. No other clinical drug-drug interaction studies have been conducted with conjugated estrogens.

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 preparations (*Hypericum perforatum*), 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.

### **Clinical Studies**

#### ***Women's Health Initiative Studies.***

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of Premarin tablets (0.625 mg conjugated estrogens per day) alone or the use of PREMPRO™ tablets (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate per day) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of Premarin tablets or PREMPRO on menopausal symptoms.

NDA 20-216/S-052

Page 6

The Premarin tablets-only substudy results have not been reported. The estrogen plus progestin substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the “global index.” Results of the estrogen plus progestin substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years, are presented in Table 1 below:

| <b>Table 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN PLUS PROGESTIN SUBSTUDY OF WHI<sup>a</sup></b>  |  |  |                     |
|---|--|--|---------------------|
| Event <sup>c</sup>  | Relative Risk<br>Prempro vs Placebo<br>at 5.2 Years<br>(95% CI*) | Placebo<br>n = 8102                      | Prempro<br>n = 8506 |
|   |  | Absolute Risk per 10,000 Women-<br>years |                     |
| CHD events  | 1.29 (1.02-1.63)   | 30                                       | 37                  |
| <i>Non-fatal MI</i>   | 1.32 (1.02-1.72)   | 23                                       | 30                  |
| <i>CHD death</i>  | 1.18 (0.70-1.97)   | 6  | 7                   |
| Invasive breast cancer <sup>b</sup>   | 1.26 (1.00-1.59)   | 30                                       | 38                  |
| Stroke  | 1.41 (1.07-1.85)   | 21                                       | 29                  |
| Pulmonary embolism  | 2.13 (1.39-3.25)   | 8  | 16                  |
| Colorectal cancer   | 0.63 (0.43-0.92)   | 16                                       | 10                  |
| Endometrial cancer  | 0.83 (0.47-1.47)   | 6  | 5                   |
| Hip fracture  | 0.66 (0.45-0.98)   | 15                                       | 10                  |
| Death due to causes other<br>than the events above  | 0.92 (0.74-1.14)   | 40                                       | 37                  |
| Global Index <sup>c</sup>   | 1.15 (1.03-1.28)   | 151                                      | 170                 |
|   |  |  |                     |
| Deep vein thrombosis <sup>d</sup>   | 2.07 (1.49-2.87)   | 13                                       | 26                  |
| Vertebral fractures <sup>d</sup>  | 0.66 (0.44-0.98)   | 15                                       | 9                   |
| Other osteoporotic<br>fractures <sup>d</sup>  | 0.77 (0.69-0.86)   | 170                                      | 131                 |
| <sup>a</sup> adapted from JAMA, 2002; 288:321-333<br><sup>b</sup> includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer<br><sup>c</sup> 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, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes<br><sup>d</sup> not included in Global Index<br>* nominal confidence intervals unadjusted for multiple looks and multiple comparisons |  |  |                     |

For those outcomes included in the “global index”, the absolute excess risks per 10,000 women-years in the group treated with PREMPRO were 7 more CHD events, 8 more strokes, 8 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. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

NDA 20-216/S-052

Page 7

***Women's Health Initiative Memory Study.***

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of PREMPRO (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNING**, and **WARNINGS, Dementia.**)

**INDICATIONS AND USAGE**

Premarin (conjugated estrogens) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae.

**CONTRAINDICATIONS**

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

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
5. Active or recent (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. Premarin Vaginal Cream should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for Premarin Vaginal Cream in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogen and progestins from oral contraceptives inadvertently during pregnancy. (See **PRECAUTIONS.**)

**WARNINGS**

See **BOXED WARNINGS.**

NDA 20-216/S-052

Page 8

Systemic absorption may occur with the use of Premarin Vaginal Cream. The warnings, precautions, and adverse reactions associated with oral Premarin treatment should be taken into account.

### 1. **Cardiovascular disorders.**

Estrogen and estrogen/progestin therapy have been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

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

**a. Coronary heart disease and stroke.** In the Premarin tablets substudy of the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and stroke has been observed in women receiving Premarin compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the estrogen plus progestin substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving PREMPRO compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same substudy of the WHI, an increased risk of stroke was observed in women receiving PREMPRO compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with PREMPRO (0.625 mg conjugated estrogen plus 2.5 mg medroxyprogesterone acetate per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with PREMPRO did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the PREMPRO-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one 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 PREMPRO group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

**b. Venous thromboembolism (VTE).** In the Premarin tablets substudy of the Women's Health Initiative (WHI), an increase in VTE has been observed in women receiving Premarin compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

NDA 20-216/S-052

Page 9

In the estrogen plus progestin substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving PREMPRO compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the Prempro group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

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.

## 2. **Malignant neoplasms.**

**a. Endometrial cancer.** The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

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

**b. Breast cancer.** The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) trial of estrogen plus progestin (See **CLINICAL PHARMACOLOGY, Clinical Studies**). The results from observational studies are generally consistent with those of the WHI trial.

After a mean follow-up of 5.6 years, the WHI trial reported an increased risk of breast cancer in women who took estrogen plus progestin. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen/progestin combinations, doses, or routes of administration.

NDA 20-216/S-052

Page 10

In the WHI trial of estrogen plus progestin, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen plus progestin group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups. The observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of hormone therapy compared to never users, while the estrogen plus progestin sub-study of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years.

The observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of estrogens alone or estrogens plus progestins compared to never users, while the estrogen plus progestin sub-study of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

### **3. Dementia.**

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with PREMPRO (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for PREMPRO versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for PREMPRO versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for PREMPRO was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use**.)

The results of the estrogen-alone sub-study of the Women's Health Initiative Memory Study have not been reported. It is unknown whether these findings apply to estrogen-alone therapy.

### **4. Gallbladder disease.**

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

### **5. Hypercalcemia.**

NDA 20-216/S-052

Page 11

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

#### **6. Visual abnormalities.**

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

### **PRECAUTIONS**

#### **A. General**

##### **1. *Addition of a progestin when a woman has not had a hysterectomy.***

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance.

##### **2. *Elevated blood pressure.***

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

##### **3. *Hypertriglyceridemia.***

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

##### **4. *Impaired liver function and past history of cholestatic jaundice.***

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

NDA 20-216/S-052

Page 12

**5. *Hypothyroidism.***

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T<sub>4</sub> and T<sub>3</sub> serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

**6. *Fluid retention.***

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

**7. *Hypocalcemia.***

Estrogens should be used with caution in individuals with severe hypocalcemia.

**8. *Ovarian cancer.***

The estrogen plus progestin substudy of WHI reported that after an average follow-up of 5.6 years, the relative risk for ovarian cancer for estrogen plus progestin versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

**9. *Exacerbation of endometriosis.***

Endometriosis may be exacerbated with administration of estrogen therapy.

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

**10. *Exacerbation of other conditions.***

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

**11. *Barrier contraceptives.***

Premarin Vaginal Cream exposure has been reported to weaken latex condoms. The potential for Premarin Vaginal Cream to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber should be considered.

**B. Patient Information**

Physicians are advised to discuss the contents of the PATIENT INFORMATION leaflet with patients for whom they prescribe Premarin Vaginal Cream.

**C. Laboratory Tests**

Estrogen administration should be guided by clinical response at the lowest dose for the treatment of postmenopausal vulvar and vaginal atrophy.

NDA 20-216/S-052

Page 13

#### **D. Drug/Laboratory Test Interactions**

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T<sub>4</sub> levels (by column or by radioimmunoassay) or T<sub>3</sub> levels by radioimmunoassay. T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG. Free T<sub>4</sub> and free T<sub>3</sub> concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL<sub>2</sub> cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

#### **E. Carcinogenesis, Mutagenesis, Impairment of Fertility**

(See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

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.

#### **F. Pregnancy**

Premarin Vaginal Cream should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

#### **G. Nursing Mothers**

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving the drug. Caution should be exercised when Premarin Vaginal Cream is administered to a nursing woman.

#### **H. 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 adult 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.

NDA 20-216/S-052

Page 14

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. See **INDICATIONS** and **DOSAGE AND ADMINISTRATION** sections.

### **I. Geriatric Use**

Of the total number of subjects in the estrogen plus progestin substudy of the Women's Health Initiative study, 44% (n = 7,320) were 65 years and over, while 6.6% (n = 1,095) were 75 years and over (See **CLINICAL PHARMACOLOGY, Clinical Studies**). There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age.

In the Women's Health Initiative Memory Study (WHIMS), including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with oral conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See **WARNINGS, Dementia**).

There have not been sufficient numbers of geriatric patients involved in 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.

### **ADVERSE REACTIONS**

See **BOXED WARNINGS, WARNINGS, and PRECAUTIONS**.

Systemic absorption may occur with the use of Premarin Vaginal Cream. Warnings, precautions, and adverse reactions associated with oral Premarin treatment should be taken into account.

The following additional adverse reactions have been reported with estrogen and/or progestin therapy:

1. *Genitourinary system*: Breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginitis, including vaginal candidiasis; change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; application site reactions of vulvovaginal discomfort including burning and irritation; genital pruritus; ovarian cancer; endometrial hyperplasia; endometrial cancer; precocious puberty.
2. *Breasts*: Tenderness, pain, enlargement, secretion; breast cancer; fibrocystic breast changes.
3. *Cardiovascular*: Deep and superficial venous thrombosis, pulmonary embolism, myocardial infarction, stroke; increase in blood pressure.
4. *Gastrointestinal*: Nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; pancreatitis; increased incidence of gallbladder disease; enlargement of hepatic hemangiomas.
5. *Skin*: Chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritis; rash; urticaria.

NDA 20-216/S-052

Page 15

6. *Eyes*: Retinal vascular thrombosis; intolerance to contact lenses.
7. *Central Nervous System*: Headache; migraine; dizziness; nervousness; mood disturbances; irritability; mental depression; chorea; exacerbation of epilepsy; dementia.
8. *Miscellaneous*: Increase or decrease in weight; reduced carbohydrate tolerance; glucose intolerance; aggravation of porphyria; edema; changes in libido; anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; angioedema; hypersensitivity; increased triglycerides; arthralgias; leg cramps.

### OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen/progestin containing drug products by young children. Overdosage of estrogens may cause nausea and vomiting, and withdrawal bleeding may occur in females.

### DOSAGE AND ADMINISTRATION

Use of Premarin Vaginal Cream, alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., at 3-month to 6-month intervals) to determine if treatment is still necessary (See **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

*Given cyclically for short-term use only:*

For treatment of atrophic vaginitis, or kraurosis vulvae. The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (e.g., three weeks on and one week off).

Usual Dosage Range:

½ to 2 g daily, intravaginally, depending on the severity of the condition.

Instructions For Use Of Gentle Measure™ Applicator

1. Remove cap from tube.
2. Screw nozzle end of applicator onto tube.
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 as a guideline to measure the correct dose.
4. Unscrew applicator from tube.
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.

To Cleanse: Pull plunger to remove it from barrel. Wash with mild soap and warm water.

NDA 20-216/S-052  
Page 16

DO NOT BOIL OR USE HOT WATER.

**HOW SUPPLIED**

Premarin<sup>®</sup> (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

*Combination package:* Each contains Net Wt. 1 ½ oz (42.5 g) tube with one plastic applicator calibrated in ½ g increments to a maximum of 2 g (NDC 0046-0872-93).

*Also Available —Refill package:* Each contains Net Wt. 1 ½ oz (42.5 g) tube (NDC 0046-0872-01).

**Store at room temperature (approximately 25° C).**

NDA 20-216/S-052  
Page 17

**PATIENT INFORMATION**  
**(Updated insert full date here)**

**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 Premarin Vaginal Cream. 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)?**

- Estrogens increase the chances of getting cancer of the uterus.  
  
Report any unusual vaginal bleeding right away while you are taking 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, or strokes.  
  
Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia based on a study of women age 65 years 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.

**Premarin Vaginal Cream is used to:**

- treat dryness, itching, and burning, in and around the vagina due to menopause. You and your healthcare provider should talk regularly about whether you still need treatment with Premarin Vaginal Cream to control these problems.

**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 chances 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.

NDA 20-216/S-052

Page 18

- **had a stroke or heart attack in the past year.**
- **currently have or had blood clots.**
- **currently have liver problems.**
- **are allergic to Premarin Vaginal Cream or any of its ingredients.**  
See the end of this leaflet for a list of all the ingredients in Premarin Vaginal Cream.
- **think you may be pregnant.**

#### **Tell your healthcare provider:**

- **if you are breast feeding.** The hormones in Premarin Vaginal Cream can pass into your milk.
- **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), migraine, endometriosis, lupus, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Premarin Vaginal Cream works. Premarin Vaginal Cream may also affect how your other medicines work.
- **if you are going to have surgery or will be on bedrest.** You may need to stop using Premarin Vaginal Cream.

#### **How should I use Premarin Vaginal Cream?**

The Gentle Measure™ Applicator has been specifically designed for comfortable, easy use.

1. Remove cap from tube.
2. Screw nozzle end of applicator onto tube.
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 as a guideline to measure the correct dose, as prescribed by your healthcare provider.
4. Unscrew applicator from tube.
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.

TO CLEANSE: Pull plunger to remove it from barrel. Wash with mild soap and warm water.

DO NOT BOIL OR USE HOT WATER.

NDA 20-216/S-052

Page 19

Premarin Vaginal Cream should be used at the lowest possible dose for your treatment and only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Premarin Vaginal Cream.

### **What are the possible side effects of Premarin Vaginal Cream?**

Although Premarin Vaginal Cream is only used in and around the vagina, the risks associated with Premarin tablets should be taken into account.

#### **Less common but serious side effects of estrogens include:**

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

#### **These are some of the warning signs of serious side effects:**

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

#### **Common side effects of estrogens include:**

- Headache
- Breast tenderness
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Reactions from inserting Premarin Vaginal Cream such as vaginal burning, irritation, and itching

#### **Other side effects of estrogens include:**

- High blood pressure
- Liver problems

NDA 20-216/S-052

Page 20

- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus (“fibroids”)
- Vaginal yeast infections
- Allergic Reactions

These are not all the possible side effects of Premarin Vaginal Cream. For more information, ask your healthcare provider or pharmacist.

### **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.
- See your healthcare provider right away if you get vaginal bleeding while using Premarin Vaginal Cream.
- Have a 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 health care 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.**

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. You can get more information by calling the toll free number 1-800-934-5556.

#### **HOW SUPPLIED**

Premarin<sup>®</sup> (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

*Combination package:* Each contains Net Wt. 1 ½ oz (42.5 g) tube with one plastic applicator calibrated in ½ g increments to a maximum of 2 g (NDC 0046-0872-93).

*Also Available—Refill package:* Each contains Net Wt. 1 ½ oz (42.5 g) tube (NDC 0046-0872-01).

**Store at room temperature (approximately 25° C).**

NDA 20-216/S-052  
Page 21

**Wyeth<sup>®</sup>**

Wyeth Pharmaceuticals Inc.  
Philadelphia, PA 19101

Winsert number here  
ETinsert number here  
Revised insert full date here

NDA 20-216/S-052

Page 22

# **Premarin<sup>®</sup>** (conjugated estrogens) **Vaginal Cream** in a nonliquefying base

## **Rx only**

? TEAR HERE

### **PATIENT INFORMATION**

Read this PATIENT INFORMATION before you start using Premarin Vaginal Cream and read what you get each time you refill Premarin Vaginal Cream. 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)?**

- Estrogens increase the chances of getting cancer of the uterus.

Report any unusual vaginal bleeding right away while you are taking 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, or strokes.

Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia based on a study of women age 65 years 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.

#### **Premarin Vaginal Cream is used to:**

- treat dryness, itching, and burning, in and around the vagina due to menopause.

You and your healthcare provider should talk regularly about whether you still need treatment with Premarin Vaginal Cream to control these problems.

#### **Who should not use Premarin Vaginal Cream?**

Do not start using Premarin Vaginal Cream if you:

NDA 20-216/S-052

Page 23

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.**  
Estrogens may increase the chances 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 in the past year.**
- **currently have or had blood clots.**
- **currently have liver problems.**
- **are allergic to Premarin Vaginal Cream or any of its ingredients.**  
See the end of this leaflet for a list of all the ingredients in Premarin Vaginal Cream.
- **think you may be pregnant.**

#### **Tell your healthcare provider:**

- **if you are breast feeding.** The hormones in Premarin Vaginal Cream can pass into your milk.
- **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), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Premarin Vaginal Cream works. Premarin Vaginal Cream may also affect how your other medicines work.
- **if you are going to have surgery or will be on bedrest.** You may need to stop using Premarin Vaginal Cream.

#### **How should I use Premarin Vaginal Cream?**

The Gentle Measure™ Applicator has been specifically designed for comfortable, easy use.

1. Remove cap from tube.
2. Screw nozzle end of applicator onto tube.
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 as a guideline to measure the correct dose.
4. Unscrew nozzle end of applicator onto tube.

NDA 20-216/S-052

Page 24

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.

TO CLEANSE: Pull plunger to remove it from barrel. Wash with mild soap and warm water.

DO NOT BOIL OR USE HOT WATER.

Premarin Vaginal Cream should be used at the lowest dose possible for your treatment and 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 about whether you still need treatment with Premarin Vaginal Cream.

### **What are the possible side effects of Premarin Vaginal Cream?**

Although Premarin Vaginal Cream is only used in and around vagina, the risks associated with Premarin tablets should be taken into account.

#### **Less common but serious side effects of estrogens include:**

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Dementia
- Blood clots
- Gallbladder disease
- Ovarian cancer

#### **These are some of the warning signs of serious side effects:**

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

#### **Common side effects of estrogens include:**

- Headache
- Breast tenderness
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating

NDA 20-216/S-052

Page 25

- Nausea and vomiting
- Hair loss
- Reactions from inserting Premarin Vaginal Cream such as vaginal burning, irritation, and itching

**Other side effects of estrogens include:**

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus (“fibroids”)
- Vaginal yeast infections
- Allergic reactions

These are not all the possible side effects of Premarin Vaginal Cream. For more information, ask your healthcare provider or pharmacist.

**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.
- See your healthcare provider right away if you get vaginal bleeding while using Premarin Vaginal Cream.
- Have a 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 health care 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.**

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. You can get more information by calling the toll free number 800-934-5556.

NDA 20-216/S-052  
Page 26

### HOW SUPPLIED

Premarin<sup>®</sup> (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

*Combination package:* Each contains Net Wt. 1 ½ oz (42.5 g) tube with one plastic applicator calibrated in ½ g increments to a maximum of 2 g (NDC 0046-0872-93).

*Also Available—Refill package:* Each contains Net Wt. 1 ½ oz (42.5 g) tube (NDC 0046-0872-01).

**Store at room temperature (approximately 25° C).**



This product's label may have been revised after this insert was used in production. For further product information and current package insert, please visit [www.wyeth.com](http://www.wyeth.com) or call our medical communications department toll-free at 1-800-934-5556.



# Wyeth<sup>®</sup>

Wyeth Pharmaceuticals Inc.  
Philadelphia, PA 19101

Winsert number here  
ETinsert number here  
Revised insert full date here

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20216Orig1s043**

**PRODUCT QUALITY REVIEW(S)**

CHEMIST'S REVIEW

**1. Organization**  
DRUDP HFD-580

**2. NDA Number**  
20-216

**3. Name and Address of Applicant**

Wyeth-Ayerst Laboratories  
P.O. Box 8299  
Philadelphia, PA 19101-8299

**4. Supplement**

SCF-043  
04-JUN-1998

**5. Name of Drug**

Premarin vaginal cream

**6. Nonproprietary Name**

conjugated estrogens

**7. Supplement Provides For**

[Redacted] (b) (4)

**8. Amendment**

**9. Pharmacological Category**

Treatment of atrophic vaginitis  
and kaurosis vulvae

**10. How Dispensed**

RX

**11. Related**

**12. Dosage form**

Cream

**13. Potency**

0.625 mg

**14. Chemical Name and Structure**

see USP

**15. Comments**

See next page.

**16. Conclusion and Recommendation**

This Supplement may be approved. Issue an approval letter.

**17. Name**

David T. Lin, Ph.D.  
Review Chemist

**Reviewer's Signature**

*David T. Lin*  
12/1/98

**Date**

01-DEC-1998

cc:

Orig. NDA #20-216  
HFD-580/Division File  
HFD-580/D Moore  
HFD-580/MRhee/DLin

R/D Init by: MJ Rhee

*MJRhee 12/2/98*

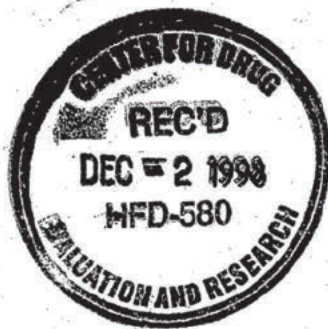
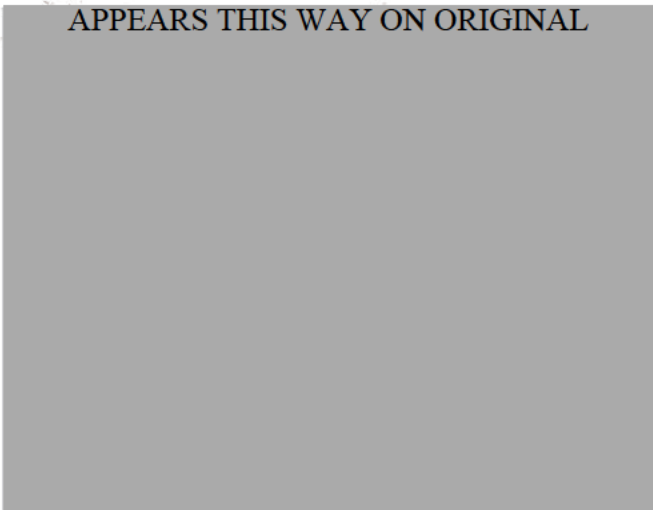
Filename: S20216.043 (doc)

manufacturing equipment has not been changed. A summary of the changes in the manufacturing method has been included in the submission. The changes are all considered minor, thus they will not be described in any detail in this review. The <sup>(b)(4)</sup> and a detailed description of the manufacturing method are included in the submission. The <sup>(b)(4)</sup> has not been changed from what was submitted in the approved original NDA (see Chem. Rev. #1; 14-JAN-1998). Although there are minor change in the manufacturing method, the in-process controls and specifications have not been changed.

(b)(4)  
(b)(4)



APPEARS THIS WAY ON ORIGINAL



**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20216Orig1s043**

**ADMINISTRATIVE AND CORRESPONDENCE**  
**DOCUMENTS**



Food and Drug Administration  
Rockville MD 20857

NDA 20-216/S-043

Wyeth-Ayerst Laboratories  
P.O. Box 8299  
Philadelphia, PA 19101-8299

JUN 18 1998

Attention: Joseph S. Sonk, Ph.D., Senior Director  
U.S. Drug Regulatory Affairs

Dear Dr. Sonk:

We acknowledge receipt of your supplemental application for the following:

|                     |                        |
|---------------------|------------------------|
| Name of Drug:       | Premarin Vaginal Cream |
| NDA Number:         | 20-216                 |
| Supplement Number:  | S-043                  |
| Date of Supplement: | June 4, 1998           |
| Date of Receipt:    | June 5, 1998           |

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on August 4, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug Products, HFD-580  
Office of Drug Evaluation II  
Attention: Document Control Room 17B-20  
5600 Fishers Lane  
Rockville, MD 20857

Sincerely,

Lana L. Pauls, M.P.H.  
Chief, Project Management Staff  
Division of Reproductive and Urologic  
Drug Products, HFD-580  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

NDA 20-216/S-043

Page 2

cc:

Original NDA 20-216/S-043

HFD-580/Div. Files

HFD-580/CSO/D. Moore

SUPPLEMENT ACKNOWLEDGEMENT

ORIGINAL

WYETH-AYERST  RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710  
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

NDA #20-216

|  |
|--|
| REVIEWS COMPLETED  |
| <i>AP</i>  |
| CSD ACTION:  |
| <input checked="" type="checkbox"/> LETTER <input type="checkbox"/> N.A. <input type="checkbox"/> MEMO |
| <i>Dr</i> <i>12/4/98</i>   |
| CSD INITIALS DATE  |

NDA NO. 20-216 REF. NO. 043  
NDA SUPPL FOR SCF SS

June 4, 1998

Lisa Rarick, M.D., Director  
Division of Reproductive and Urologic Drug Products (HFD-580)  
Room 17B-20  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

*see Chemistry Review (12/1/98) DTU 12/2/98*



**SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED**

Dear Dr. Rarick:

Reference is made to our approved New Drug Application No. 20-216 for Premarin®, conjugated estrogens, USP, Vaginal Cream.

The purpose of this Special Supplement-Change Being Effected is to provide for



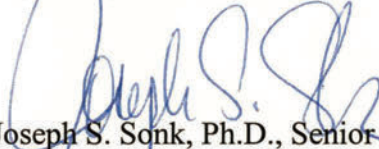
(b) (4)

Lisa Rarick, M.D.  
June 4, 1998  
Page 3

Wyeth-Ayerst hereby certifies that a field copy of these supplemental applications has been forwarded to the Philadelphia district office, the FDA home office for Wyeth-Ayerst Laboratories, as required by 21 CFR 314.71 (b).

We trust you will find this information satisfactory and that this supplemental application may be approved at your earliest convenience. Should you have any questions regarding this information, please call the undersigned at (610) 902-3740 or Sharon White at (610) 902-3784.

Sincerely,  
Wyeth-Ayerst Laboratories

  
Joseph S. Sonk, Ph.D., Senior Director  
Women's Health Care Products  
U.S. Regulatory Affairs

cc: Ms. D. Pagano, FDA District Office, Philadelphia, PA

AP 12/4/98  
Dhr