

Wyeth

April 13, 2006

Dear Pharmacist,

We are writing to update you on the latest detailed analysis regarding breast cancer from the Women's Health Initiative (WHI) estrogen-alone substudy in women who have had a hysterectomy. In the April 12, 2006, issue of the *Journal of the American Medical Association*, Stefanick ML et al for the WHI Investigators, published the centrally adjudicated results regarding breast cancer outcomes for the double-blind portion of the trial after an average of 7.1 years of follow-up.¹ These data include important information for women who are appropriate candidates for estrogen therapy with PREMARIN[®] (conjugated estrogens tablets, USP), which is indicated for the relief of moderate to severe menopausal symptoms and the concomitant prevention of postmenopausal osteoporosis.

In this report, study authors concluded that postmenopausal women with hysterectomy treated with conjugated estrogens 0.625 mg did not have an increased incidence of breast cancer. The authors also noted the possibility of a protective effect of conjugated estrogens against breast cancer incidence in three groups of patients—women with a low overall five-year Gail Risk Score,* women with no first-degree relatives with breast cancer, and women with no prior history of benign breast disease. Further analysis found those women who were adherent to their conjugated estrogens regimen had a statistically significant decrease in breast cancer risk compared to women taking placebo. In addition to these findings, the researchers examined data on mammograms and found that by the end of the first year, the percentage of mammograms requiring short-term follow-up was significantly higher in the conjugated estrogens group compared to the placebo group (436 [9.2%] of 4718 vs. 260 [5.5%] of 4763, respectively; $P < 0.001$). The centrally adjudicated data are presented in Table 1, below.

We would also like to notify you of two other articles published April 10th in the *Archives of Internal Medicine*. The first article summarized venous thrombosis data from the WHI estrogen-alone substudy (Curb JD, et al. *Arch Intern Med.* 2006;166:772-780). The reported increased risk of venous thrombosis is consistent with data from other studies and with information in the current product labeling. The other article summarized findings from the Black Women's Health Study, a questionnaire-based observational study of women age 40 years or older (Rosenberg L, et al. *Arch Intern Med.* 2006;166:760-765). Overall, the latter report indicated a statistically significant increase in breast cancer risk among black women. This study is based on self-reported data from women who used various preparations of estrogen, progestin, or combination hormone therapy for various periods of time.

Wyeth believes all of these findings should be included as part of the individualized benefit/risk assessment and the discussion between menopausal women and health care professionals.

Wyeth continues to support the appropriate use of hormone therapy for its approved indications—the relief of moderate to severe menopausal symptoms, such as hot flashes, night sweats and vaginal dryness, and the concomitant prevention of postmenopausal osteoporosis—and recommends that therapy be taken at the lowest effective dose for the shortest duration consistent with treatment goals and risks for the individual woman.

Women who are considering the use of estrogen therapy should be counseled about the potential risks cited in the enclosed product labeling. The PREMARIN[®] Family offers extensive clinical experience and one of the largest safety databases available, providing you and your patients with current, comprehensive information upon which to base appropriate treatment decisions.

If you have any questions about this information, you may contact Wyeth Global Medical Communications at 1-800-934-5556.

*The Gail Risk Score incorporates age, history of benign breast disease, age at menarche, age at first live birth, race/ethnicity, and number of relatives (mothers and sisters) with breast cancer.

Important Safety Information

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. (See *WARNINGS, Malignant neoplasms, Endometrial cancer* in the Prescribing Information.)

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See *WARNINGS, Cardiovascular disorders and Dementia* in the Prescribing Information.)

The Women's Health Initiative (WHI) study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated estrogens (0.625 mg) relative to placebo. (See *CLINICAL PHARMACOLOGY, Clinical Studies* and *WARNINGS, Cardiovascular disorders* in the Prescribing Information.)

The WHI study 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 conjugated estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo. (See *CLINICAL PHARMACOLOGY, Clinical Studies* and *WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer* in the Prescribing Information.)

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 5.2 years of treatment with conjugated estrogens alone and during 4 years of treatment with conjugated estrogens combined with medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See *CLINICAL PHARMACOLOGY, Clinical Studies, WARNINGS, Dementia* and *PRECAUTIONS, Geriatric Use* in the Prescribing Information.)

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.

PREMARIN® (conjugated estrogens tablets, USP) is indicated in the treatment of moderate to severe vasomotor symptoms associated with menopause, the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause, and the prevention of postmenopausal osteoporosis.

PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate tablets) is indicated in women with a uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause, the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause, and the prevention of postmenopausal osteoporosis.

When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.

In a clinical trial, the most commonly reported ($\geq 5\%$) adverse events for PREMARIN that were statistically different than placebo included vaginal moniliasis, vaginitis, vaginal bleeding, dysmenorrhea, and leg cramps. In a clinical trial, the most commonly reported ($\geq 5\%$) adverse events for PREMPRO 0.45 mg/1.5 mg and 0.625 mg/2.5 mg that were statistically different than placebo were mastalgia, vaginal bleeding, vaginal moniliasis, leg cramps, dysmenorrhea, breast enlargement, and vaginitis. In a clinical trial, there was no difference in the commonly reported ($\geq 5\%$) adverse events for women taking PREMPRO 0.3 mg/1.5 mg compared to those taking placebo.

PREMARIN and PREMPRO should not be used under any of the following conditions or circumstances: undiagnosed abnormal genital bleeding; known, suspected, or a history of breast cancer; known or suspected estrogen-dependent neoplasia; active venous thromboembolism or a history of this condition; active or recent arterial thromboembolism; liver dysfunction or disease; in patients with a known hypersensitivity to their ingredients; known or suspected pregnancy.

Please see enclosed Prescribing Information.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Camardo', written in a cursive style.

Joseph S. Camardo, M.D.
Senior Vice President, Global Medical Affairs and
North American Medical Director for Wyeth Pharmaceuticals

1. Stefanick ML, Anderson GL, Margolis KL, et al, for the WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA*. 2006;295:1647-1657.

Table 1: Key Findings from the Estrogen-Alone Study on Breast Cancer as Reported by the WHI Study Investigators

Outcome	Conjugated estrogens alone (n=5,310)	Placebo (n=5,429)	HR (95% CI)*
Total breast cancer†	129 (0.34)	161 (0.42)	0.82 (0.65-1.04)
invasive	104 (0.28)	133 (0.34)	0.80 (0.62-1.04)
in situ	25 (0.07)	30 (0.08)	0.86 (0.51-1.40)
SEER stage‡			
Localized	65 (0.18)	98 (0.25)	0.69 (0.51-0.95)
Regional	35 (0.09)	31 (0.08)	1.15 (0.71-1.86)
Missing	3 (0.01)	4 (0.01)	0.78 (0.17-3.50)
Histology‡			
Ductal	61 (0.16)	88 (0.23)	0.71 (0.52-0.99)
Lobular	18 (0.05)	12 (0.03)	1.56 (0.75-3.24)
Ductal and Lobular	12 (0.03)	12 (0.03)	1.00 (0.45-2.23)
Tubular	1 (<0.01)	4 (0.01)	NA
Other	12 (0.03)	16 (0.04)	0.76 (0.36-1.61)
Missing	0	1 (<0.01)	NA
Morphology, grade‡			
Well differentiated	19 (0.05)	26 (0.07)	0.74 (0.41-1.33)
Moderately differentiated	31 (0.08)	52 (0.13)	0.61 (0.39-0.96)
Poorly differentiated	26 (0.07)	35 (0.09)	0.77 (0.46-1.29)
Anaplastic	3 (0.01)	3 (0.01)	NA
Missing	25 (0.07)	17 (0.04)	0.73 (0.35-1.53)
Receptor Status‡			
Estrogen-receptor Assay			
Positive	72 (0.19)	95 (0.25)	0.78 (0.57-1.06)
Negative	19 (0.05)	21 (0.005)	0.92 (0.49-1.72)
Borderline	1 (<0.01)	0	NA
Missing	12 (0.03)	17 (0.04)	0.73 (0.35-1.53)
Progesterone-receptor Assay			
Positive	56 (0.15)	70 (0.18)	0.82 (0.58-1.17)
Negative	33 (0.09)	42 (0.11)	0.80 (0.51-1.27)
Borderline	2 (0.01)	2 (0.01)	NA
Missing	13 (0.03)	19 (0.05)	0.71 (0.35-1.43)

Note: Conjugated estrogens/placebo presented as number of patients (annualized %);

Overall study population: n=5,310 for conjugated estrogens and n=5,429 for placebo.

*From unweighted Cox proportional hazard models, stratified by age and Dietary Modification trial randomization assignment.

†Total breast cancer is the first of either invasive or in situ breast cancer.

‡Invasive subtypes of breast cancer.

Mean duration of patient follow-up was 7.1 years.