PREMARIN®
(conjugated estrogens tablets, USP)

Rx only

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. (See **WARNINGS, Malignant Neoplasms, Endometrial cancer**.)

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders** and **Probable Dementia**.)

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 **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**.)

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

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

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders** and **Probable Dementia**.)

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**.)

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. (See **CLINICAL STUDIES** and **WARNINGS, Malignant Neoplasms, Breast cancer**.)

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

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

PREMARIN® (conjugated estrogens tablets, USP) for oral administration contains 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 as concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin. Tablets for oral administration are available in 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg strengths of conjugated estrogens.

PREMARIN 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg tablets also contain the following inactive ingredients: calcium phosphate tribasic, carnauba wax, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, powdered cellulose, sucrose, and titanium dioxide.

— 0.3 mg tablets also contain: D&C Yellow No. 10 and FD&C Blue No. 2.

— 0.45 mg tablets also contain: FD&C Blue No. 2.

— 0.625 mg tablets also contain: FD&C Blue No. 2 and FD&C Red No. 40.

— 0.9 mg tablets also contain: D&C Red No. 30 and D&C Red No. 7.

— 1.25 mg tablets also contain: black iron oxide, D&C Yellow No. 10 and FD&C Yellow No. 6.

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

PREMARIN 1.25 mg tablets	USP Dissolution Test 4
PREMARIN 0.3 mg, 0.45 mg and 0.625 mg tablets	USP Dissolution Test 5
PREMARIN 0.9 mg tablets	USP Dissolution Test 6

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 in the peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Pharmacokinetics

A. Absorption

Conjugated estrogens are water-soluble and are well-absorbed from the gastrointestinal tract after release from the drug formulation. The PREMARIN tablet releases conjugated estrogens slowly over several hours. Table 1 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens following administration of 1 x 0.625 mg and 1 x 1.25 mg tablets to healthy postmenopausal women.

The pharmacokinetics of PREMARIN 0.45 mg and 1.25 mg tablets were assessed following a single dose with a high-fat breakfast and with fasting administration. The C_{max} and AUC of

estrogens were altered approximately 3 to 13 percent. The changes to C_{max} and AUC are not considered clinically meaningful.

TABLE 1. PHARMACOKINETIC PARAMETERS FOR PREMARIN®

Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 1 x 0.625 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	87 (33)	9.6 (33)	50.7 (35)	5557 (59)
Baseline-adjusted estrone	64 (42)	9.6 (33)	20.2 (40)	1723 (52)
Equilin	31 (38)	7.9 (32)	12.9 (112)	602 (54)
Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 1 x 0.625 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Total Estrone	2.7 (43)	6.9 (25)	26.7 (33)	75 (52)
Baseline-adjusted total estrone	2.5 (45)	6.9 (25)	14.8 (35)	46 (48)
Total Equilin	1.8 (56)	5.6 (45)	11.4 (31)	27 (56)
Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 1 x 1.25 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	124 (30)	10.0 (32)	38.1 (37)	6332 (44)
Baseline-adjusted estrone	102 (35)	10.0 (32)	19.7 (48)	3159 (53)
Equilin	59 (43)	8.8 (36)	10.9 (47)	1182 (42)
Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 1 x 1.25 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Total Estrone	4.5 (39)	8.2 (58)	26.5 (40)	109 (46)
Baseline-adjusted total estrone	4.3 (41)	8.2 (58)	17.5 (41)	87 (44)
Total equilin	2.9 (42)	6.8 (49)	12.5 (34)	48 (51)

B. 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.

C. Metabolism

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

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

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

F. Drug Interactions
Data from a single-dose drug-drug interaction study involving 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 (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

CLINICAL STUDIES

Effects on vasomotor symptoms

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2,805 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups, receiving either placebo or conjugated estrogens, with or without medroxyprogesterone acetate. Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least seven moderate to severe hot flushes daily, or at least 50 moderate to severe hot flushes during the week before randomization. PREMARIN (0.3 mg, 0.45 mg, and 0.625 mg tablets) was shown to be statistically better than placebo at weeks 4 and 12 for relief of both the frequency and severity of moderate to severe vasomotor symptoms. Table 2 shows the adjusted mean number of hot flushes in the PREMARIN 0.3 mg, 0.45 mg, and 0.625 mg and placebo treatment groups over the initial 12-week period.

TABLE 2. SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY – MEAN VALUES AND COMPARISONS BETWEEN THE ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP: PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, LAST OBSERVATION CARRIED FORWARD (LOCF)

Treatment (No. of Patients)	----------No. of Hot Flushes/Day----------			
Time Period (week)	Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SD	p-Values vs. Placebo[a]
0.625 mg CE (n = 27)				
4	12.29 ± 3.89	1.95 ± 2.77	-10.34 ± 4.73	<0.001
12	12.29 ± 3.89	0.75 ± 1.82	-11.54 ± 4.62	<0.001
0.45 mg CE (n = 32)				
4	12.25 ± 5.04	5.04 ± 5.31	-7.21 ± 4.75	<0.001
12	12.25 ± 5.04	2.32 ± 3.32	-9.93 ± 4.64	<0.001
0.3 mg CE (n = 30)				
4	13.77 ± 4.78	4.65 ± 3.71	-9.12 ± 4.71	<0.001
12	13.77 ± 4.78	2.52 ± 3.23	-11.25 ± 4.60	<0.001
Placebo (n = 28)				
4	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 4.71	-
12	11.69 ± 3.87	5.71 ± 5.22	-5.98 ± 4.60	-

a: Based on analysis of covariance with treatment as factor and baseline as covariate.

Effects on vulvar and vaginal atrophy

Results of vaginal maturation indexes at cycles 6 and 13 showed that the differences from placebo were statistically significant ($p < 0.001$) for all treatment groups (conjugated estrogens alone and conjugated estrogens/medroxyprogesterone acetate treatment groups).

Effects on bone mineral density

Health and Osteoporosis, Progestin and Estrogen (HOPE) Study

The HOPE study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy postmenopausal women with an intact uterus. Subjects (mean age 53.3 ± 4.9 years) were 2.3 ± 0.9 years on average since menopause and took one 600-mg tablet of elemental calcium (Caltrate™) daily. Subjects were not given Vitamin D supplements. They were treated with PREMARIN 0.625 mg, 0.45 mg, 0.3 mg, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L_2 to L_4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

Intent-to-treat subjects
All active treatment groups showed significant differences from placebo in each of the four BMD endpoints at cycles 6, 13, 19, and 26. The mean percent increases in the primary efficacy measure (L_2 to L_4 BMD) at the final on-therapy evaluation (cycle 26 for those who completed and the last available evaluation for those who discontinued early) were 2.46 percent with 0.625 mg, 2.26 percent with 0.45 mg, and 1.13 percent with 0.3 mg. The placebo group showed a mean percent decrease from baseline at the final evaluation of 2.45 percent. These results show that the lower dosages of PREMARIN were effective in increasing L_2 to L_4 BMD compared with placebo, and therefore support the efficacy of the lower doses.

The analysis for the other three BMD endpoints yielded mean percent changes from baseline in femoral trochanter that were generally larger than those seen for L_2 to L_4, and changes in femoral neck and total body that were generally smaller than those seen for L_2 to L_4. Significant differences between groups indicated that each of the PREMARIN treatments was more effective than placebo for all three of these additional BMD endpoints. With regard to femoral neck and total body, the active treatment groups all showed mean percent increases in BMD, while placebo treatment was accompanied by mean percent decreases. For femoral trochanter, each of the PREMARIN dose groups showed a mean percent increase that was significantly greater than the small increase seen in the placebo group. The percent changes from baseline to final evaluation are shown in Table 3.

TABLE 3. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LOCF

Region Evaluated Treatment Group[a]	No. of Subjects	Baseline (g/cm^2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs Placebo
L_2 to L_4 BMD				
0.625	83	1.17 ± 0.15	2.46 ± 0.37	<0.001
0.45	91	1.13 ± 0.15	2.26 ± 0.35	<0.001
0.3	87	1.14 ± 0.15	1.13 ± 0.36	<0.001
Placebo	85	1.14 ± 0.14	-2.45 ± 0.36	
Total Body BMD				
0.625	84	1.15 ± 0.08	0.68 ± 0.17	<0.001
0.45	91	1.14 ± 0.08	0.74 ± 0.16	<0.001
0.3	87	1.14 ± 0.07	0.40 ± 0.17	<0.001
Placebo	85	1.13 ± 0.08	-1.50 ± 0.17	
Femoral Neck BMD				
0.625	84	0.91 ± 0.14	1.82 ± 0.45	<0.001
0.45	91	0.89 ± 0.13	1.84 ± 0.44	<0.001
0.3	87	0.86 ± 0.11	0.62 ± 0.45	<0.001
Placebo	85	0.88 ± 0.14	-1.72 ± 0.45	
Femoral Trochanter BMD				
0.625	84	0.78 ± 0.13	3.82 ± 0.58	<0.001
0.45	91	0.76 ± 0.12	3.16 ± 0.56	0.003
0.3	87	0.75 ± 0.10	3.05 ± 0.57	0.005
Placebo	85	0.75 ± 0.12	0.81 ± 0.58	

a: Identified by dosage (mg) of PREMARIN or placebo.

Figure 1 shows the cumulative percentage of subjects with changes from baseline equal to or greater than the value shown on the x-axis.

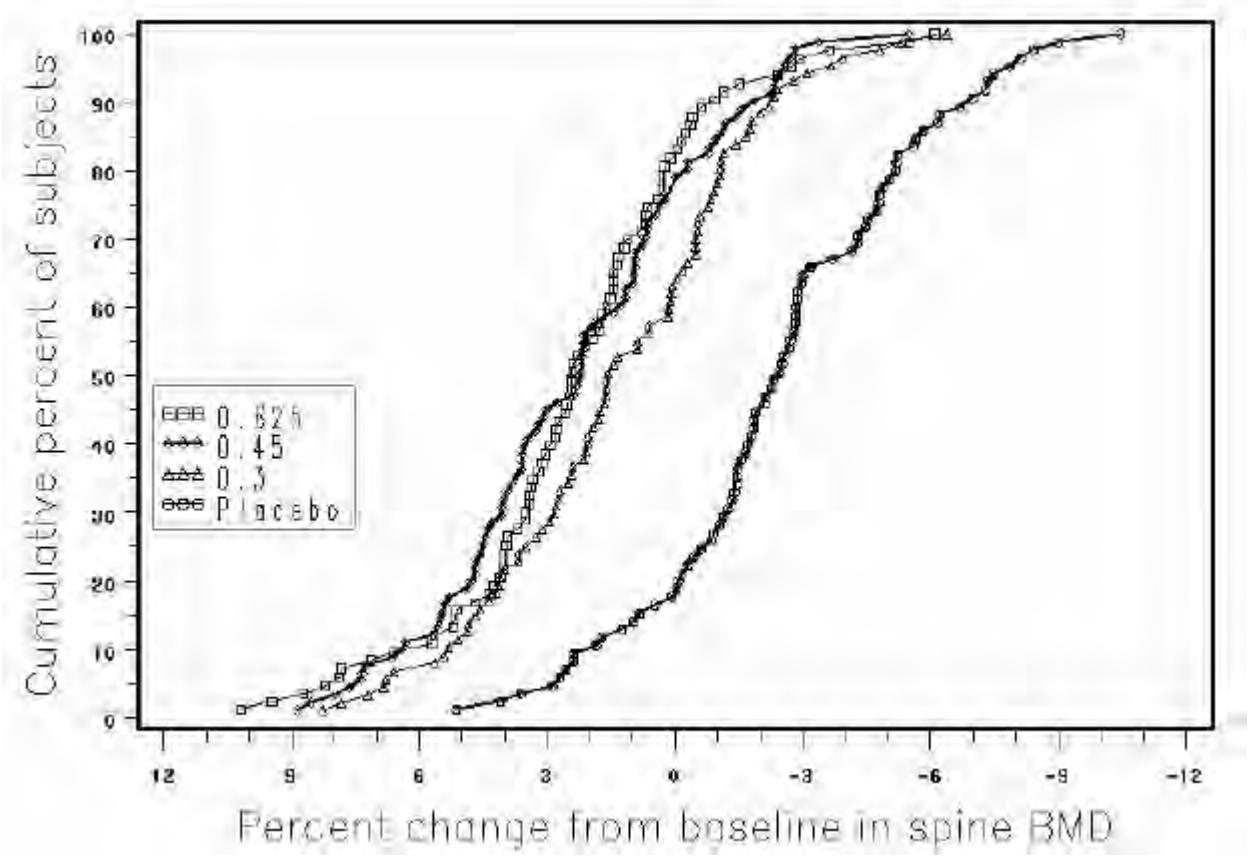

Figure 1. CUMULATIVE PERCENT OF SUBJECTS WITH CHANGES FROM BASELINE IN SPINE BMD OF GIVEN MAGNITUDE OR GREATER IN PREMARIN® AND PLACEBO GROUPS

The mean percent changes from baseline in L_2 to L_4 BMD for women who completed the bone density study are shown with standard error bars by treatment group in Figure 2. Significant differences between each of the PREMARIN dosage groups and placebo were found at cycles 6, 13, 19, and 26.

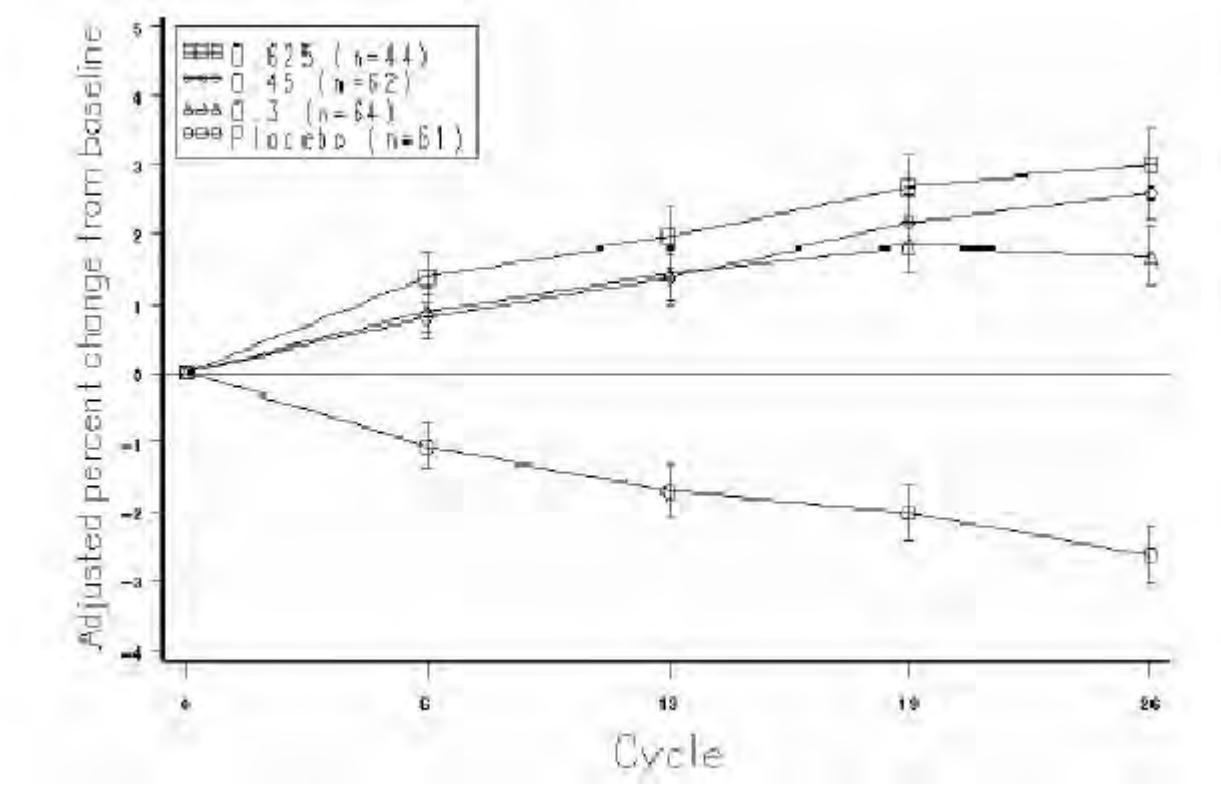

Figure 2. ADJUSTED MEAN (SE) PERCENT CHANGE FROM BASELINE AT EACH CYCLE IN SPINE BMD: SUBJECTS COMPLETING IN PREMARIN® GROUPS AND PLACEBO

The bone turnover markers serum osteocalcin and urinary N-telopeptide significantly decreased ($p < 0.001$) in all active-treatment groups at cycles 6, 13, 19, and 26 compared with the placebo group. Larger mean decreases from baseline were seen with the active groups than with the placebo group. Significant differences from placebo were seen less frequently in urine calcium.

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease [(CHD) defined as nonfatal MI, silent MI and CHD death], with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. These substudies did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in Table 4.

TABLE 4. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[b])	CE n = 5,310 Absolute Risk per 10,000 Women-Years	Placebo n = 5,429 Absolute Risk per 10,000 Women-Years
CHD events[c]	0.95 (0.78-1.16)	54	57
Non-fatal MI[c]	*0.91 (0.73-1.14)*	*40*	*43*
CHD death[c]	*1.01 (0.71-1.43)*	*16*	*16*
All Stroke[c]	1.33 (1.05-1.68)	45	33
Ischemic stroke[c]	*1.55 (1.19-2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06-2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90-2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62-1.04)	28	34
Colorectal cancer[e]	1.08 (0.75-1.55)	17	16
Hip fracture[c]	0.65 (0.45-0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47-0.72)	35	59
Total fractures[c,d]	0.71 (0.64-0.80)	144	197
Death due to other causes[e,f]	1.08 (0.88-1.32)	53	50
Overall mortality[c,d]	1.04 (0.88-1.22)	79	75
Global Index[g]	1.02 (0.92-1.13)	206	201

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[c] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[d] Not included in Global Index.
[e] Results are based on an average follow-up of 6.8 years.
[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
[g] A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was

reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess was present in all subgroups of women examined.

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50 to 59 years of age, a non-significant trend toward reduced risk for CHD [hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)] and overall mortality [HR 0.71 (95 percent CI, 0.46-1.11)].

WHI Estrogen Plus Progestin Substudy

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

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

Results of the estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 5. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

TABLE 5. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN PLUS PROGESTIN SUBSTUDY OF WHI AT AN AVERAGE OF 5.6 YEARS[a,b]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[c])	CE/MPA n = 8,506 Absolute Risk per 10,000 Women-Years	Placebo n = 8,102 Absolute Risk per 10,000 Women-Years
CHD events	1.23 (0.99-1.53)	41	34
Non-fatal MI	*1.28 (1.00-1.63)*	*31*	*25*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All strokes	1.31 (1.03-1.68)	33	25
Ischemic Stroke	*1.44 (1.09-1.90)*	*26*	*18*
Deep vein thrombosis[d]	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer[e]	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer[d]	0.81 (0.48-1.36)	6	7
Cervical cancer[d]	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures[d]	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures[d]	0.71 (0.59-0.85)	44	62
Total fractures[d]	0.76 (0.69-0.83)	152	199
Overall mortality[f]	1.00 (0.83-1.19)	52	52
Global Index[g]	1.13 (1.02-1.25)	184	165

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

Timing of the initiation of estrogen 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 0.69 (95 percent CI, 0.44-1.07)].

Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83–2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer disease (AD), vascular dementia (VaD) and mixed type (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, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

The WHIMS estrogen plus progestin ancillary study 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; 18 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 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 type (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, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

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, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

INDICATIONS AND USAGE

PREMARIN therapy is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms due to menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).
6. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

   The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg per day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU per day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

PREMARIN therapy should not be used in individuals with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of breast cancer except in appropriately selected patients being treated for metastatic disease.
3. Known or suspected estrogen-dependent neoplasia.
4. Active DVT, PE, or a history of these conditions.
5. Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions.
6. Known anaphylactic reaction or angioedema to PREMARIN tablets.
7. Known liver dysfunction or disease.
8. Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders.
9. Known or suspected pregnancy.

WARNINGS

See **BOXED WARNINGS**.

1. Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy.

An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy.

Should any of these events occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

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

a. Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). (See **CLINICAL STUDIES**.) The increase in risk was demonstrated in year 1 and persisted. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).

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

b. Coronary heart disease

In the WHI estrogen-alone substudy, no overall effect on CHD events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo. (See **CLINICAL STUDIES**.)

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women 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.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established 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 the subsequent years. Two thousand three hundred and twenty one (2,321) women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-

up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in the HERS, the HERS II, and overall.

c. Venous thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE), was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women years). The increase in VTE risk was demonstrated during the first 2 years. (See **CLINICAL STUDIES**.) Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE(0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See **CLINICAL STUDIES**.) 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.

2. Malignant Neoplasms

a. Endometrial cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

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

b. Breast cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg)-alone was not

associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80) (See **CLINICAL STUDIES**).

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24 and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups. (See **CLINICAL STUDIES**.)

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and 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.

c. Ovarian cancer
The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77 – 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen plus progestin 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.

3. Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 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. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). 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 **PRECAUTIONS, Geriatric Use**.)

4. Gallbladder Disease

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

5. Hypercalcemia

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

6. Visual Abnormalities

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

7. Anaphylactic Reaction and Angioedema

Cases of anaphylaxis, which developed within minutes to hours after taking PREMARIN and require emergency medical management, have been reported in the postmarketing setting. Skin (hives, pruritis, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) involvement has been noted.

Angioedema involving the tongue, larynx, face, hands, and feet requiring medical intervention has occurred postmarketing in patients taking PREMARIN. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop an anaphylactic reaction

with or without angioedema after treatment with PREMARIN should not receive PREMARIN again.

8. Hereditary Angioedema

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

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 an increased risk of breast cancer.

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.

3. Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

4. Hepatic impairment and/or past history of cholestatic jaundice

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

5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention

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

7. Hypocalcemia

Estrogen therapy should be used with caution in individuals with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

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

9. 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.

B. Patient Information
Physicians are advised to discuss the contents of the **PATIENT INFORMATION** leaflet with patients for whom they prescribe PREMARIN.

C. Laboratory Tests
Serum FSH and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

Laboratory parameters may be useful in guiding dosage for the treatment of hypoestrogenism due to hypogonadism, castration and primary ovarian failure.

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 anti-factor 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) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), SHBG, leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.
5. Impaired glucose tolerance.

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 should not be used during pregnancy. (See **CONTRAINDICATIONS**.) There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

G. Nursing Mothers
PREMARIN should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogens. Caution should be exercised when PREMARIN 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 stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding. In boys, estrogen treatment may modify the normal pubertal process and induce gynecomastia. (See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**.)

I. Geriatric Use
There have not been sufficient numbers of geriatric patients involved in studies utilizing PREMARIN to determine whether those over 65 years of age differ from younger subjects in their response to PREMARIN.

The Women's Health Initiative Study

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age. (See **CLINICAL STUDIES**.)

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age. (See **CLINICAL STUDIES**.)

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia**.)

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 **CLINICAL STUDIES** and **WARNINGS, Probable Dementia**.)

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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During the first year of a 2-year clinical trial with 2,333 postmenopausal women between 40 and 65 years of age (88 percent Caucasian), 1,012 women were treated with conjugated estrogens and 332 were treated with placebo. Table 6 summarizes adverse events that occurred at a rate of ≥ 5 percent.

TABLE 6. NUMBER (%) OF PATIENTS REPORTING ≥ 5 PERCENT TREATMENT EMERGENT ADVERSE EVENTS

	--Conjugated Estrogens Treatment Group--			
Body System	0.625 mg	0.45 mg	0.3 mg	Placebo
Adverse event	(n = 348)	(n = 338)	(n = 326)	(n = 332)
Any adverse event	323 (93%)	305 (90%)	292 (90%)	281 (85%)
Body as a Whole				
Abdominal pain	56 (16%)	50 (15%)	54 (17%)	37 (11%)
Accidental injury	21 (6%)	41 (12%)	20 (6%)	29 (9%)
Asthenia	25 (7%)	23 (7%)	25 (8%)	16 (5%)
Back pain	49 (14%)	43 (13%)	43 (13%)	39 (12%)
Flu syndrome	37 (11%)	38 (11%)	33 (10%)	35 (11%)
Headache	90 (26%)	109 (32%)	96 (29%)	93 (28%)
Infection	61 (18%)	75 (22%)	74 (23%)	74 (22%)
Pain	58 (17%)	61 (18%)	66 (20%)	61 (18%)
Digestive System				
Diarrhea	21 (6%)	25 (7%)	19 (6%)	21 (6%)
Dyspepsia	33 (9%)	32 (9%)	36 (11%)	46 (14%)
Flatulence	24 (7%)	23 (7%)	18 (6%)	9 (3%)
Nausea	32 (9%)	21 (6%)	21 (6%)	30 (9%)
Musculoskeletal System				
Arthralgia	47 (14%)	42 (12%)	22 (7%)	39 (12%)
Leg cramps	19 (5%)	23 (7%)	11 (3%)	7 (2%)
Myalgia	18 (5%)	18 (5%)	29 (9%)	25 (8%)
Nervous System				
Depression	25 (7%)	27 (8%)	17 (5%)	22 (7%)
Dizziness	19 (5%)	20 (6%)	12 (4%)	17 (5%)
Insomnia	21 (6%)	25 (7%)	24 (7%)	33 (10%)
Nervousness	12 (3%)	17 (5%)	6 (2%)	7 (2%)
Respiratory System				
Cough increased	13 (4%)	22 (7%)	14 (4%)	14 (4%)
Pharyngitis	35 (10%)	35 (10%)	40 (12%)	38 (11%)
Rhinitis	21 (6%)	30 (9%)	31 (10%)	42 (13%)
Sinusitis	22 (6%)	36 (11%)	24 (7%)	24 (7%)
Upper respiratory infection	42 (12%)	34 (10%)	28 (9%)	35 (11%)
Skin and Appendages				
Pruritus	14 (4%)	17 (5%)	16 (5%)	7 (2%)
Urogenital System				
Breast pain	38 (11%)	41 (12%)	24 (7%)	29 (9%)
Leukorrhea	18 (5%)	22 (7%)	13 (4%)	9 (3%)
Vaginal hemorrhage	47 (14%)	14 (4%)	7 (2%)	0
Vaginal moniliasis	20 (6%)	18 (5%)	17 (5%)	6 (2%)
Vaginitis	24 (7%)	20 (6%)	16 (5%)	4 (1%)

Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of PREMARIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System
Abnormal uterine bleeding, dysmenorrhea or pelvic pain, increase in size of uterine leiomyomata, vaginitis, including vaginal candidiasis, change in cervical secretion, ovarian cancer, endometrial hyperplasia, endometrial cancer, leukorrhea.

Breast
Tenderness, enlargement, pain, discharge, galactorrhea, fibrocystic breast changes, breast cancer, gynecomastia in males.

Cardiovascular
Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

Gastrointestinal
Nausea, vomiting, abdominal pain, bloating, cholestatic jaundice, increased incidence of gallbladder disease, pancreatitis, enlargement of hepatic hemangiomas, ischemic colitis.

Skin
Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, loss of scalp hair, hirsutism, pruritus, rash.

Eyes
Retinal vascular thrombosis, intolerance to contact lenses.

Central Nervous System
Headache, migraine, dizziness, mental depression, nervousness, mood disturbances, irritability, exacerbation of epilepsy, dementia, possible growth potentiation of benign meningioma.

Miscellaneous
Increase or decrease in weight, glucose intolerance, aggravation of porphyria, edema, arthralgias, leg cramps, changes in libido, urticaria, exacerbation of asthma, increased triglycerides, hypersensitivity.

Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

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

DOSAGE AND ADMINISTRATION

When estrogen therapy is prescribed for a postmenopausal woman with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (for example at 3-month to 6-month intervals) to determine if treatment is still necessary. Adequate diagnostic measures, such as directed or random endometrial sampling, when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

PREMARIN may be taken without regard to meals.

1. For treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy due to menopause:

   When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

   Patients should be treated with the lowest effective dose. Generally, women should be started at 0.3 mg PREMARIN daily. Subsequent dosage adjustment may be made based upon the individual patient response. This dose should be periodically reassessed by the healthcare provider.

   PREMARIN therapy may be given continuously, with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug), as is medically appropriate on an individualized basis.

2. For prevention of postmenopausal osteoporosis:

   When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be considered only for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. Patients should be treated with the lowest effective dose. Generally, women should be started at 0.3 mg PREMARIN daily. Subsequent dosage adjustment may be made based upon the individual clinical and bone mineral density responses. This dose should be periodically reassessed by the healthcare provider.

   PREMARIN therapy may be given continuously, with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug), as is medically appropriate on an individualized basis.

3. For treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:

   Female hypogonadism — 0.3 mg or 0.625 mg daily, administered cyclically (e.g., three weeks on and one week off). Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium.

   In clinical studies of delayed puberty due to female hypogonadism, breast development was induced by doses as low as 0.15 mg. The dosage may be gradually titrated upward at 6-to-12 month intervals as needed to achieve appropriate bone age advancement and eventual epiphyseal closure. Clinical studies suggest that doses of 0.15 mg, 0.3 mg, and 0.6 mg are associated with mean ratios of bone age advancement to chronological age

progression (ΔBA/ΔCA) of 1.1, 1.5, and 2.1, respectively. (PREMARIN in the dose strength of 0.15 mg is not available commercially). Available data suggest that chronic dosing with 0.625 mg is sufficient to induce artificial cyclic menses with sequential progestin treatment and to maintain bone mineral density after skeletal maturity is achieved.

Female castration or primary ovarian failure — 1.25 mg daily, cyclically. Adjust dosage, upward or downward, according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

4. For treatment of breast cancer, for palliation only, in appropriately selected women and men with metastatic disease:

   Suggested dosage is 10 mg three times daily, for a period of at least three months.

5. For treatment of advanced androgen-dependent carcinoma of the prostate, for palliation only:

   1.25 mg to 2 x 1.25 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.

HOW SUPPLIED
PREMARIN® (conjugated estrogens tablets, USP)

— Each oval green tablet contains 0.3 mg, in bottles of 100 (NDC 0046-1100-81) and 1,000 (NDC 0046-1100-91).

— Each oval blue tablet contains 0.45 mg, in bottles of 100 (NDC 0046-1101-81).

— Each oval maroon tablet contains 0.625 mg, in bottles of 100 (NDC 0046-1102-81) and 1,000 (NDC 0046-1102-91).

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

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

The appearance of these tablets is a trademark of Wyeth LLC.

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

Dispense in a well-closed container, as defined in the USP.

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PATIENT INFORMATION
PREMARIN®
(conjugated estrogens tablets, USP)

Read this PATIENT INFORMATION before you start taking PREMARIN and read what you get each time you refill your PREMARIN prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

- Using estrogen-alone increases your chance of getting cancer of the uterus (womb)
  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 estrogen-alone to prevent heart disease, heart attacks, strokes, or dementia (decline of brain function)
- Using estrogen-alone may increase your chances of getting strokes or blood clots
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age or older
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older
- You and your healthcare provider should talk regularly about whether you still need treatment with PREMARIN

What is PREMARIN?
PREMARIN is a medicine that contains a mixture of estrogen hormones.

What is PREMARIN used for?

PREMARIN is used after menopause to:

- **Reduce moderate to severe hot flashes**

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

When the estrogen levels begin dropping, some women get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe.

- **Treat menopausal changes in and around the vagina**

  You and your healthcare provider should talk regularly about whether you still need treatment with PREMARIN to control these problems. If you use PREMARIN only to treat your menopausal changes in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.
- **Help reduce your chances of getting osteoporosis (thin weak bones)**

  Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use PREMARIN only to prevent osteoporosis due to menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

  Weight-bearing exercise, like walking or running, and taking calcium (1500 mg per day of elemental calcium) and vitamin D (400-800 IU per day) supplements may also lower your chances for getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

  You and your healthcare provider should talk regularly about whether you still need treatment with PREMARIN.

PREMARIN is also used to:

- **Treat certain conditions in women before menopause if their ovaries do not make enough estrogen naturally**
- **Ease symptoms of certain cancers that have spread through the body, in men and women**

Who should not take PREMARIN?
Do not start taking PREMARIN if you:

- **Have unusual vaginal bleeding**

- **Currently have or have had certain cancers**

  Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should take PREMARIN.

- **Had a stroke or heart attack**
- **Currently have or have had blood clots**
- **Currently have or have had liver problems**
- **Have been diagnosed with a bleeding disorder**
- **Are allergic to PREMARIN tablets or any of its ingredients**

  See the list of ingredients in PREMARIN at the end of this leaflet.

- **Think you may be pregnant**

Tell your healthcare provider:

- **If you have any unusual vaginal bleeding**

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

- **About all of your medical problems**

  Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **About all the medicines you take**

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

- **If you are going to have surgery or will be on bedrest**

  You may need to stop taking PREMARIN.

- **If you are breast feeding**

  The hormones in PREMARIN can pass into your breast milk.

How should I take PREMARIN?

- Take one PREMARIN tablet at the same time each day

- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time
- Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with PREMARIN
- If you see something that resembles a tablet in your stool, talk to your healthcare provider.

What are the possible side effects of PREMARIN?

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- Heart attack
- Stroke
- Blood clots
- Dementia
- Breast cancer
- Cancer of the lining of the uterus (womb)
- Cancer of the ovary
- High blood pressure
- High blood sugar
- Gallbladder disease
- Liver problems
- Enlargement of benign tumors of the uterus (“fibroids”)
- Severe allergic reactions

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

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

Less serious, but common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach or abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

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

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

- Talk with your healthcare provider regularly about whether you should continue taking PREMARIN
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb)
- See your healthcare provider right away if you get vaginal bleeding while taking PREMARIN

- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often

- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease

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

Keep PREMARIN out of the reach of children.

This leaflet provides a summary of the most important information about PREMARIN. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about PREMARIN that is written for health professionals. You can get more information by calling the toll free number 1-800-438-1985.

What are the ingredients in PREMARIN?
PREMARIN contains a mixture of conjugated estrogens, which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin.

PREMARIN 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg tablets also contain the following inactive ingredients: calcium phosphate tribasic, carnauba wax, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, powdered cellulose, sucrose and titanium dioxide.

The tablets come in different strengths and each strength tablet is a different color. The color ingredients are:

— 0.3 mg tablet (green color): D&C Yellow No. 10 and FD&C Blue No. 2.

— 0.45 mg tablet (blue color): FD&C Blue No. 2.

— 0.625 mg tablet (maroon color): FD&C Blue No. 2 and FD&C Red No. 40.

— 0.9 mg tablet (white color): D&C Red No. 30 and D&C Red No. 7.

— 1.25 mg tablet (yellow color): black iron oxide, D&C Yellow No. 10, and FD&C Yellow No. 6.

The appearance of these tablets is a trademark of Wyeth LLC.

Store at Controlled Room Temperature 20° to 25°C (68° to 77°F).

This product's label may have been updated. For current package insert and further product information, please visit www.pfizerpro.com or call our medical communications department toll-free at 1-800-438-1985.

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