Premarin®
(conjugated estrogens tablets, USP)

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. (See **WARNINGS, Malignant neoplasms, Endometrial cancer**.)

CARDIOVASCULAR AND OTHER RISKS

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

The estrogen-alone substudy of the Women's Health Initiative (WHI) reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) per day relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders**.)

The estrogen-plus-progestin substudy of the 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 5.6 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders** and **Malignant neoplasms, Breast cancer**.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of 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 CE 0.625 mg alone and during four years of treatment with 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, Dementia** and **PRECAUTIONS, Geriatric Use**.)

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

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, hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, 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 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg and 1.25 mg tablets	USP Dissolution Test pending

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 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 soluble in water 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 3-13%. 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 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.

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 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

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

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]
0.3 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% with 0.625 mg, 2.26% with 0.45 mg, and 1.13% with 0.3 mg. The placebo group showed a mean percent decrease from baseline at the final evaluation of 2.45%. 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

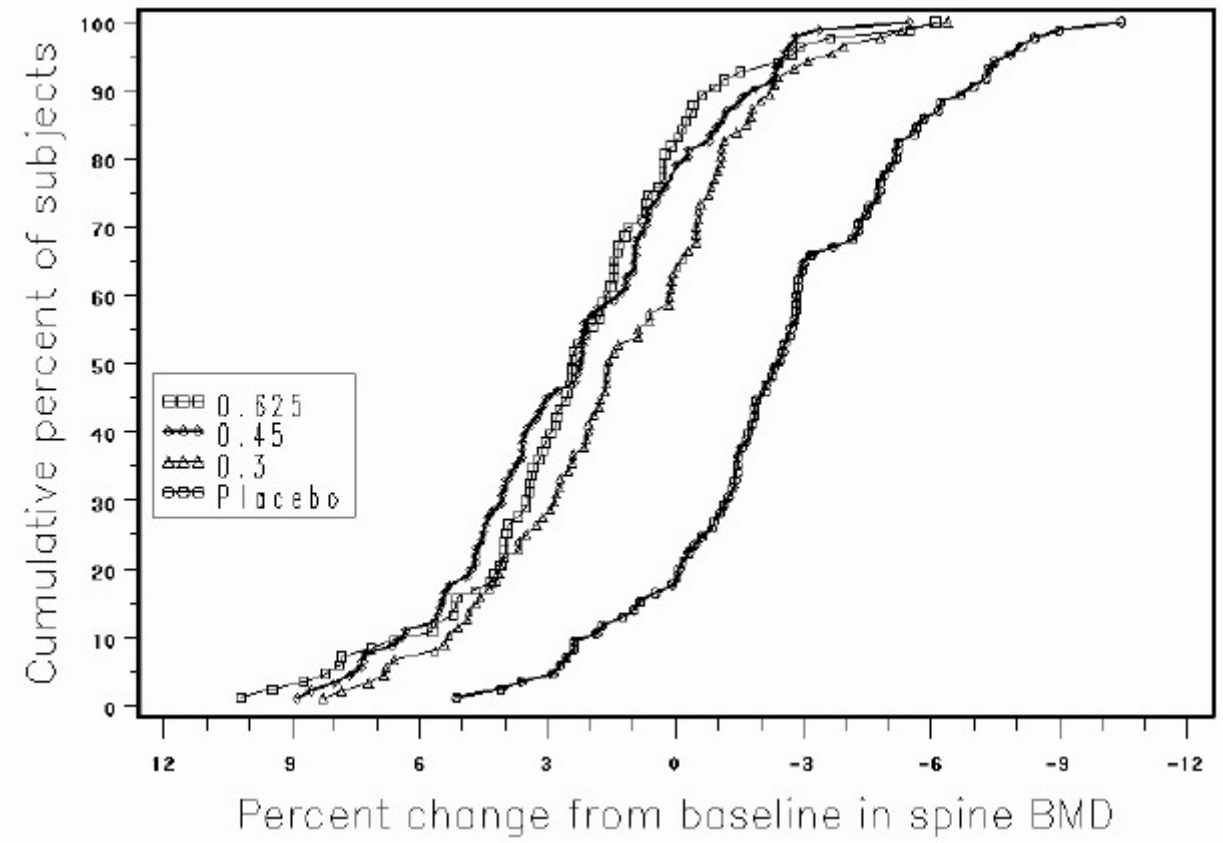
TABLE 3. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LOCF

Region Evaluated Treatment Group[a]	No. of Subjects	Baseline (g/cm^2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs Placebo
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.

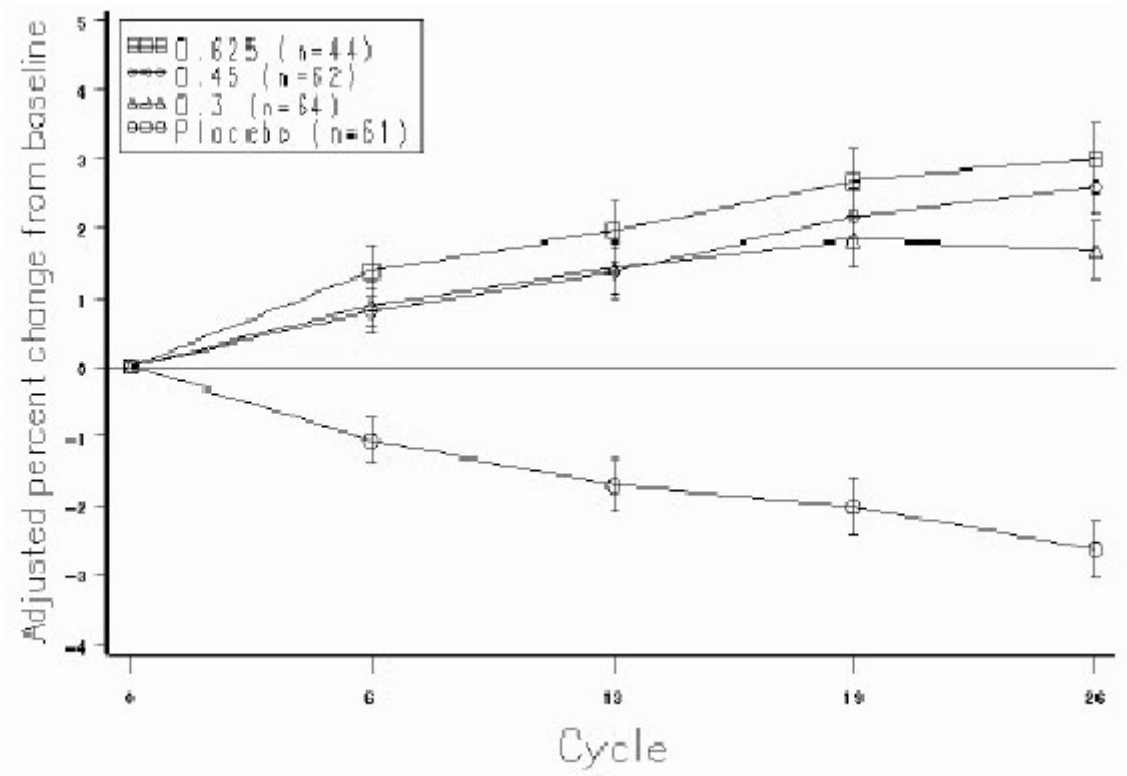
Figure 1 shows the cumulative percentage of subjects with changes from baseline equal to or greater than the value shown on the x-axis.

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 oral conjugated estrogens (CE 0.625 mg) alone or in combination with medroxyprogesterone acetate (CE 0.625 mg/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) (nonfatal myocardial infarction (MI), silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in CE/MPA), colorectal cancer, hip fracture, or death due to other causes. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The 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 age of 63 years, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other) after an average follow-up of 6.8 years, are presented in **Table 4** below.

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

Event	Relative Risk CE vs. Placebo (95% nCI[a])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-years	
CHD events[b]	0.95 (0.79-1.16)	53	56
Non-fatal MI[b]	*0.91 (0.73-1.14)*	*40*	*43*
CHD death[b]	*1.01 (0.71-1.43)*	*16*	*16*
Stroke[c]	1.39 (1.10-1.77)	44	32
Deep vein thrombosis[b,d]	1.47 (1.06-2.06)	23	15
Pulmonary embolism[b]	1.37 (0.90-2.07)	14	10
Invasive breast cancer[b]	0.80 (0.62-1.04)	28	34
Colorectal cancer[c]	1.08 (0.75-1.55)	17	16
Hip fracture[c]	0.61 (0.41-0.91)	11	17
Vertebral fractures[c,d]	0.62 (0.42-0.93)	11	17
Total fractures[c,d]	0.70 (0.63-0.79)	139	195
Death due to other causes[c,e]	1.08 (0.88-1.32)	53	50
Overall mortality[c,d]	1.04 (0.88–1.22)	81	78
Global Index[c,f]	1.01 (0.91-1.12)	192	190

[a]Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[b]Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

[c]Results are based on an average follow-up of 6.8 years.

[d]Not included in Global Index.

[e]All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.

[f]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 were 12 more strokes while the absolute risk reduction per 10,000 women-years was six fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant two events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Final adjudicated results for CHD events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) in women receiving CE alone compared with placebo (see **Table 4**).

The estrogen-plus-progestin substudy was also stopped early. According to the predefined stopping rule, after an average follow-up of 5.2 years of treatment, the increased risk of 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 (RR 1.15, 95% nCI 1.03-1.28).

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/MPA were six more CHD events, seven more strokes, ten more PEs, and eight more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were seven fewer colorectal cancers and five fewer hip fractures. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Results of the estrogen plus progestin substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.8% Black, 5.4% Hispanic, 3.9% Other), are presented in Table 5 below. 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]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[b])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-years	
CHD events	1.24 (1.00-1.54)	39	33
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 (1.02-1.68)	31	24
Ischemic Stroke	*1.44 (1.09-1.90)*	*26*	*18*

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

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[b])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-years	
Deep vein thrombosis	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer[c]	1.24 (1.01-1.54)	41	33
Invasive colorectal cancer	0.56 (0.38-0.81)	9	16
Endometrial cancer	0.81 (0.48-1.36)	6	7
Cervical cancer	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures	0.71 (0.59-0.85)	44	62
Total fractures	0.76 (0.69-0.83)	152	199

[a]Results are based on centrally adjudicated data. Mortality data was not part of the adjudicated data; however, data at 5.2 years of follow-up showed no difference between the groups in terms of all-cause mortality (RR 0.98, 95% nCI 0.82-1.18).

[b]Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[c]Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.

Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45%, age 65 to 69 years; 36%, 70 to 74 years; 19%, 75 years of age and older) to evaluate the effects of CE 0.625 mg daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen-alone group was 1.49 (95% CI 0.83–2.66) compared to placebo. It is unknown whether these findings apply to

younger postmenopausal women. (See **BOXED WARNINGS**, **WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use**.)

The estrogen-plus-progestin WHIMS substudy enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47%, age 65 to 69 years; 35%, 70 to 74 years; 18%, 75 years of age and older) to evaluate the effects of CE/MPA 0.625 mg conjugated estrogens/2.5 mg medroxyprogesterone acetate daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of four years, 40 women in the estrogen-plus-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 1.21–3.48) compared to placebo.

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% 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 **BOXED WARNINGS**, **WARNINGS**, **Dementia** and **PRECAUTIONS**, **Geriatric Use**.)

INDICATIONS AND USAGE
Premarin therapy is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the 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 for whom non-estrogen medications are not considered to be appropriate. (See **CLINICAL STUDIES**.)

   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/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/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

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

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.
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 tablets should not be used in patients with known hypersensitivity to their ingredients.
8. Known or suspected pregnancy. There is no indication for Premarin 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**.

1. Cardiovascular disorders

Estrogen-alone therapy has been associated with an increased risk of stroke and deep vein thrombosis (DVT).

Estrogen-plus-progestin therapy has been associated with an increased risk of myocardial infarction as well as stroke, venous thrombosis and pulmonary embolism.

Should any of these events 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. Stroke

In the estrogen-alone substudy of the Women's Health Initiative (WHI) study, a statistically significant increased risk of stroke was reported in women receiving CE 0.625 mg daily

compared to women receiving placebo (44 vs. 32 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, a statistically significant increased risk of stroke was reported in women receiving CE/MPA 0.625 mg/2.5 mg daily compared to women receiving placebo (31 vs. 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted.

b. Coronary heart disease
In the estrogen-alone substudy of WHI, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or death, due to CHD) was reported in women receiving estrogen alone compared to placebo. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, no statistically significant increase of CHD events was reported in women receiving CE/MPA compared to women receiving placebo (39 vs. 33 per 10,000 women years). An increase in relative risk was demonstrated in year one, 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) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with CE/MPA 0.625 mg conjugated estrogens/2.5 mg medroxyprogesterone acetate daily demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/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/MPA -treated group than in the placebo group in year one, 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 CE/MPA group and the placebo group in the HERS, the 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 risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

c. Venous thromboembolism (VTE)
In the estrogen-alone substudy of WHI, the risk of VTE (DVT and pulmonary embolism [PE]), was reported to be increased for women taking conjugated estrogens (30 vs. 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 vs. 15 per 10,000 women years). The increase in VTE risk was demonstrated during the first two years. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, a statistically significant 2-fold greater rate of VTE was reported in women receiving CE/MPA compared to women receiving placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and PE (18 vs. 8 per 10,000 women years) were also demonstrated. The increase in VTE risk was demonstrated 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 with an intact uterus 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 the 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-plus-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

In some studies, 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) (see **CLINICAL STUDIES**). The results from observational studies are generally consistent with those of the WHI clinical trial.

Observational studies have also reported an increased risk of breast cancer for estrogen-plus-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-plus-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-plus-progestin combinations, doses, or routes of administration.

In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer (RR 0.80, 95 % nCI 0.62-1.04).

In the estrogen-plus-progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer. In this substudy, prior use of estrogen alone or estrogen-plus-progestin combination hormone therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24 (95% nCI 1.01-1.54), and the absolute risk was

41 vs. 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo, respectively. 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 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.

3. Dementia
In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to CE (0.625 mg daily) or placebo. In the estrogen-plus-progestin WHIMS substudy, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo.

In the estrogen-alone substudy, 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 vs. placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for CE alone vs. placebo was 37 vs. 25 cases per 10,000 women-years.

In the estrogen-plus-progestin substudy, after an average follow-up of four years, 40 women in the estrogen-plus-progestin group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestin vs. placebo was 2.05 (95% CI 1.21-3.48). The absolute risk of probable dementia for CE/MPA vs. placebo was 45 vs. 22 cases per 10,000 women-years.

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% CI 1.19-2.60).Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **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 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 during 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. In the HOPE study, the mean percent increase from baseline in serum triglycerides after one year of treatment with Premarin 0.625 mg, 0.45 mg, and 0.3 mg compared with placebo were 34.3, 30.2, 25.1, and 10.7, respectively. After two years of treatment, the mean percent changes were 47.6, 32.5, 19.0, and 5.5, respectively.

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.

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_4 and T_3 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 vs. placebo was 1.58 (95% nCI 0.77 – 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin vs. placebo was 4.2 vs. 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for 10 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.

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 patients 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
Estrogen administration should be initiated at the lowest dose for the treatment of postmenopausal moderate-to-severe vasomotor symptoms and moderate-to-severe symptoms of postmenopausal vulvar and vaginal atrophy and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH). 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. 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_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, 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 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 the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. 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

Of the total number of subjects in the estrogen-alone substudy of the Women's Health Initiative (WHI) study, 46% (n=4,943) were 65 years and over, while 7.1% (n=767) were 75 years and over. There was a higher relative risk (CE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over.

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg daily) or placebo. After an average follow-up of 5.2 years, the relative risk (CE vs. placebo) of probable dementia was 1.49 (95% CI 0.83-2.66). The absolute risk of developing probable dementia with estrogen alone was 37 vs. 25 cases per 10,000 women-years with placebo.

Of the total number of subjects in the estrogen-plus-progestin substudy of the Women's Health Initiative study, 44% (n=7,320) were 65–74 years of age, while 6.6% (n=1,095) were 75 years and over. There was a higher relative risk (CE/MPA vs. placebo) of non-fatal stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen-plus-progestin combination group compared to the placebo group was 75 vs. 24 per 10,000 women-years and 52 vs. 12 per 10,000 women years, respectively.

In the estrogen-plus-progestin WHIMS substudy, a population of 4,532 postmenopausal women, aged 65 to 79 years, was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo. In the estrogen-plus-progestin group, after an average follow-up of four years, the relative risk (CE/MPA vs. placebo) of probable dementia was 2.05 (95% CI 1.21-3.48).The absolute risk of developing probable dementia with CE/MPA was 45 vs. 22 cases per 10,000 women-years with placebo.

Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer’s disease.

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% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS, Dementia**.)

With respect to efficacy in the approved indications, 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.

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. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

During the first year of a 2-year clinical trial with 2,333 postmenopausal women between 40 and 65 years of age (88% 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%.

TABLE 6. NUMBER (%) OF PATIENTS REPORTING ≥ 5% 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%)

TABLE 6. NUMBER (%) OF PATIENTS REPORTING ≥ 5% 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)
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%)

TABLE 6. NUMBER (%) OF PATIENTS REPORTING ≥ 5% 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)
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%)

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

1. Genitourinary system
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting, dysmenorrhea
Increase in size of uterine leiomyomata
Vaginitis, including vaginal candidiasis
Change in amount of cervical secretion
Change in cervical ectropion
Ovarian cancer
Endometrial hyperplasia
Endometrial cancer

2. Breasts
Tenderness, enlargement, pain, discharge, galactorrhea
Fibrocystic breast changes
Breast cancer

3. Cardiovascular
Deep and superficial venous thrombosis
Pulmonary embolism
Thrombophlebitis
Myocardial infarction
Stroke
Increase in blood pressure

4. Gastrointestinal
Nausea, vomiting
Abdominal cramps, bloating
Cholestatic jaundice
Increased incidence of gallbladder disease

Pancreatitis
Enlargement of hepatic hemangiomas

5. Skin
Chloasma or melasma that may persist when drug is discontinued
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Loss of scalp hair
Hirsutism
Pruritus, rash

6. Eyes
Retinal vascular thrombosis
Intolerance to contact lenses

7. Central Nervous System
Headache
Migraine
Dizziness
Mental depression
Chorea
Nervousness
Mood disturbances
Irritability
Exacerbation of epilepsy
Dementia

8. Miscellaneous
Increase or decrease in weight
Reduced carbohydrate tolerance
Aggravation of porphyria
Edema
Arthralgias
Leg cramps
Changes in libido
Urticaria, angioedema, anaphylactoid/anaphylactic reactions
Hypocalcemia
Exacerbation of asthma
Increased triglycerides

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

DOSAGE AND ADMINISTRATION

When estrogen 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 (e.g., at 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For women with 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.

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 associated with the 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 for whom non-estrogen medications are not considered to be appropriate. 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 yellow tablet contains 1.25 mg, in bottles of 100 (NDC 0046-1104-81) and 1,000 (NDC 0046-1104-91).

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

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

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

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

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

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

PATIENT INFORMATION
(Updated Rev date)

Premarin®

(conjugated estrogens tablets, USP)

Read this PATIENT INFORMATION before you start taking Premarin and read what you get each time you refill Premarin. 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, strokes, or dementia.Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens, with or without 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.

What is Premarin?

Premarin is a medicine that contains a mixture of estrogen hormones.

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. You and your healthcare provider should talk regularly about whether you still need treatment with Premarin.
- **treat moderate to severe dryness, itching, and burning, 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 dryness, itching, and burning 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 from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with Premarin.Weight-bearing exercise, like walking or running, and taking calcium and vitamin D 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.

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

Tell your healthcare provider:

- **if you are breast feeding.** The hormones in Premarin 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 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 estrogens.

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.

What are the possible side effects of Premarin?

Less common but serious side effects 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 include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

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

These are not all the possible side effects of Premarin. 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?

- 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. In general, the addition of a progestin is recommended for women with a uterus to reduce the chance of getting cancer of the uterus.
- See your healthcare provider right away if you get vaginal bleeding while taking Premarin.
- 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 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 800-934-5556.

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, hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, 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 Pharmaceuticals.

This product's label may have been updated. For current package insert and further product information, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

Wyeth®

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