â

PREMPRO™
(conjugated estrogens/medroxyprogesterone acetate tablets)
PREMPHASE®
(conjugated estrogens/medroxyprogesterone acetate tablets)

℞ only

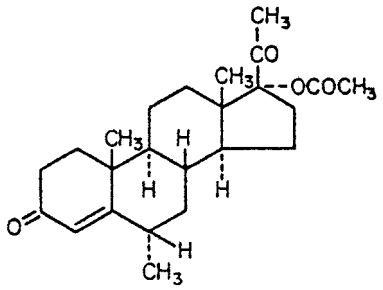
DESCRIPTION

PREMPRO therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin® tablets and 2.5 mg or 5 mg of medroxyprogesterone acetate (MPA) for oral administration.

PREMPHASE therapy consists of two separate tablets, a maroon Premarin tablet containing 0.625 mg of conjugated estrogens that is taken orally on days 1 through 14 and a light-blue tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate (MPA) that is taken orally on days 15 through 28.

The conjugated equine estrogens found in Premarin tablets are a mixture of sodium estrone sulfate and sodium equilin sulfate. They contain as concomitant components, as sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol and 17 β-dihydroequilin.

Medroxyprogesterone acetate is a derivative of progesterone. It is a white to off-white, odorless, crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water. The chemical name for MPA is pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. Its molecular formula is $C_{24}H_{34}O_4$, with a molecular weight of 386.53. Its structural formula is:



PREMPRO 2.5 mg
Each peach tablet for oral administration contains 0.625 mg conjugated estrogens, 2.5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, red ferric oxide.

PREMPRO 5 mg
Each light-blue tablet for oral administration contains 0.625 mg conjugated estrogens, 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Blue No. 2.

PREMPHASE
Each maroon Premarin tablet for oral administration contains 0.625 mg of conjugated estrogens and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, titanium dioxide, FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40. These tablets comply with USP Drug Release Test 1.

Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens and 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Blue No. 2.

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 μg 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 gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Postmenopausal estrogen therapy acts to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Parenterally administered medroxyprogesterone acetate (MPA) inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, although available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses. MPA may achieve its beneficial effect on the endometrium in part by decreasing nuclear estrogen receptors and suppression of epithelial DNA synthesis in endometrial tissue. Androgenic and anabolic effects of MPA have been noted, but the drug is apparently devoid of

significant estrogenic activity.

Pharmacokinetics

Absorption

Conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. However, PREMPRO and PREMPHASE contain a formulation of medroxyprogesterone acetate (MPA) that is immediately released and conjugated estrogens that are slowly released over several hours. MPA is well absorbed from the gastrointestinal tract. Table 1 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens, and medroxyprogesterone acetate following administration of 0.625 mg/2.5 mg and 0.625 mg/5 mg tablets to healthy postmenopausal women.

Food-Effect: Single dose studies in healthy, postmenopausal women were conducted to investigate any potential drug interaction when PREMPRO or PREMPHASE is administered with a high fat breakfast. Administration with food decreased the C_{max} of total estrone by 18 to 34% and increased total equilin C_{max} by 38% compared to the fasting state, with no other effect on the rate or extent of absorption of other conjugated or unconjugated estrogens. Administration with food approximately doubles MPA C_{max} and increases MPA AUC by approximately 20 to 30%.

Dose Proportionality: The C_{max} and AUC values for MPA observed in two separate pharmacokinetic studies conducted with PREMPRO or PREMPHASE 2 x 0.625 mg/2.5 mg and 2 x 0.625 mg /5 mg tablets exhibited nonlinear dose proportionality; doubling the MPA dose from 2 x 2.5 to 2 x 5.0 mg increased the mean C_{max} and AUC by 3.2 and 2.8 folds, respectively. The apparent clearance (Cl/F) of MPA obtained with 2 x 0.625 mg/5 mg tablets was lower than that observed with 2 x 0.625 mg/2.5 mg tablets.

Table 1. PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE), AND MEDROXYPROGESTERONE ACETATE (MPA)

DRUG	2 x 0.625 mg CE/2.5 mg MPA Combination Tablets (n=54)				2 x 0.625 mg CE/5 mg MPA Combination Tablets (n=51)			
PK Parameter Geometric Mean (SD)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{½}$** (h)	**AUC** (pg•h/mL)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{½}$** (h)	**AUC** (pg•h/mL)
Unconjugated Estrogens								
Estrone	175 (41)	7.6 (1.8)	31.6 (7.4)	5358 (1840)	124 (53)	10 (3.5)	62.2 (85.2)	6303 (2542)
BA*-Estrone	159 (41)	7.6 (1.8)	16.9 (5.8)	3313 (1310)	104 (51)	10 (3.5)	26.0 (25.9)	3136 (1598)
Equilin	71 (22)	5.8 (2.0)	9.9 (3.5)	951 (413)	54 (23)	8.9 (3.0)	15.5 (8.2)	1179 (540)
PK Parameter Geometric Mean (SD)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{½}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{½}$** (h)	**AUC** (ng•h/mL)
Conjugated Estrogens								
Total Estrone	6.6 (2.5)	6.1 (1.7)	20.7 (7.0)	116 (68)	6.3(3.0)	9.1 (2.6)	23.6(8.4)	151 (63)
BA* -Total Estrone	6.4 (2.5)	6.1 (1.7)	15.4 (5.2)	100 (57)	6.2 (3.0)	9.1 (2.6)	20.6(7.3)	139 (56)
Total Equilin	5.1 (2.3)	4.6 (1.6)	11.4 (2.9)	50 (35)	4.2 (2.2)	7.0 (2.5)	17.2(22.6)	72(36)
Medroxyprogesterone Acetate	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{½}$** (h)	**Cl/F** (L/h/kg)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{½}$** (h)	**Cl/F** (L/h/kg)
MPA	1.5 (0.6)	2.8 (1.5)	37.6 (11.2)	2.3 (0.7)	4.8 (1.5)	2.4 (1.2)	46.3 (18.0)	1.6 (0.5)

BA* = Baseline Adjusted
$t_{½}$ = terminal-phase disposition half-life (0.693/λz)
C_{max} = peak plasma concentration
AUC = total area under the curve
t_{max} = time peak concentration occurs
Cl/F = apparent oral clearance

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 concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. MPA is approximately 90% bound to plasma proteins but does not bind to SHBG.

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 resorption. 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. Metabolism and elimination of MPA occurs primarily in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Most metabolites of MPA are excreted as glucuronide conjugates with only minor amounts excreted as sulfates.

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

Drug Interactions
Data from a single-dose drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs is 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 rifampicin 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 the endometrium.
In a 1-year clinical trial of 1376 women (average age 54.0 ± 4.6 years) randomized to PREMPRO 0.625 mg/2.5 mg (Group A, n=340), PREMPRO 0.625 mg/5 mg (Group B, n=338), PREMPHASE 0.625 mg/5 mg (Group C, n=351), or Premarin 0.625 mg alone (n=347), results of evaluable biopsies at 12 months (n=279 for Group A, 274 for Group B, 277 for Group C, and 283 for Premarin alone) showed a reduced risk of endometrial hyperplasia in the two PREMPRO treatment groups (less than 1%) and in the PREMPHASE treatment group (less than 1%; 1% when focal hyperplasia was included) compared to the Premarin group (8%; 20% when focal hyperplasia was included). See Table 2.

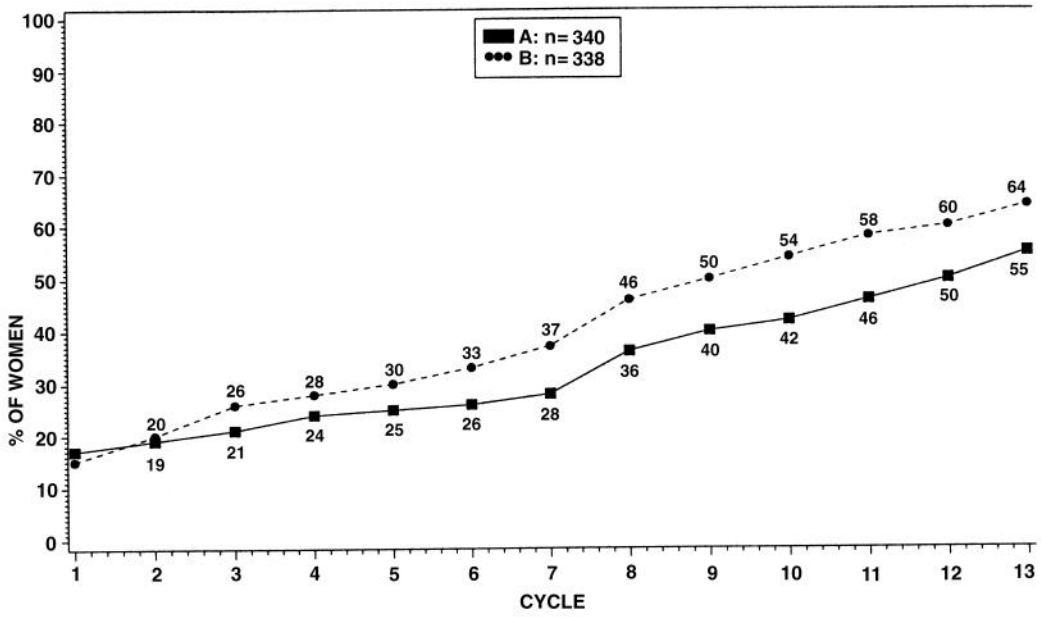
Table 2. INCIDENCE OF ENDOMETRIAL HYPERPLASIA AFTER ONE YEAR OF TREATMENT

	---------- Groups ----------			
Patient	PREMPRO 0.625 mg/2.5 mg	PREMPRO 0.625 mg/5 mg	PREMPHASE 0.625 mg/5 mg	Premarin 0.625 mg
Total number of patients	340	338	351	347
Number of patients with evaluable biopsies	279	274	277	283
No. (%) of patients with biopsies				
• all focal and non-focal hyperplasia	2 (<1)*	0 (0)*	3 (1)*	57 (20)
• excluding focal cystic hyperplasia	2 (<1)*	0 (0)*	1 (<1)*	25 (8)

*Significant ($p < 0.001$) in comparison with Premarin (0.625 mg) alone.

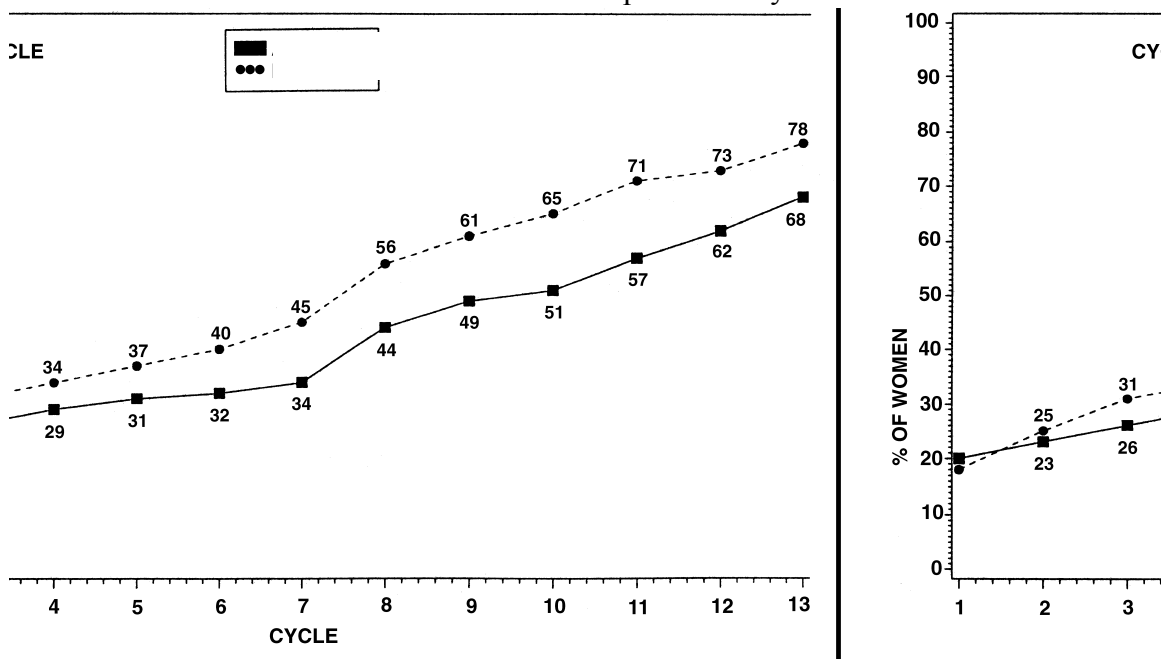
Effects on uterine bleeding or spotting.
The effects of PREMPRO on uterine bleeding or spotting, as recorded on daily diary cards, were evaluated in this same clinical trial. Results are shown in Figures 1 and 2.

Figure 1. Patients with Cumulative Amenorrhea Over Time
(Percentage of Women With No Bleeding or
Spotting at a Given Cycle Through Cycle 13), Intent-To-Treat Population



Group A: PREMARIN 0.625 mg + MPA 2.5 mg
Group B: PREMARIN 0.625 mg + MPA 5.0 mg
Note: At each cycle, the percentage of women who were amenorrheic in that cycle and through cycle 13 is shown.

Figure 2. Patients with Cumulative Amenorrhea Over Time
(Percentage of Women With No Bleeding or Spotting at a Given Cycle Through Cycle 13)
All Patients Who Completed 13 Cycles



Group A: PREMARIN 0.625 mg + MPA 2.5 mg
Group B: PREMARIN 0.625 mg + MPA 5.0 mg
Note: At each cycle, the percentage of women who were amenorrheic in that cycle and through cycle 13 is shown.

Effects on bone mineral density.
In the 3-year, randomized, double-blind, placebo-controlled Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, the effect of Premarin 0.625 mg (conjugated estrogens tablets, USP), given alone or in combination with medroxyprogesterone acetate (MPA), on bone mineral density (BMD) was evaluated in postmenopausal women. One of the regimens evaluated was continuous combined Premarin 0.625 mg/MPA 2.5 mg.

Intent-to-treat subjects
In the intent-to-treat subjects, BMD increased significantly ($p<0.001$) compared to baseline or placebo at both the hip and the spine in women assigned to Premarin or the continuous Premarin/MPA regimen. Spinal BMD increased 3.46% among women assigned to Premarin, increased 4.87% in women assigned to the Premarin/MPA regimen, and decreased 1.81% in women assigned to placebo. At the hip, women assigned to Premarin gained 1.31%, women assigned to Premarin/MPA gained 1.94% while women assigned to placebo lost 1.62%.

Adherent subjects
In the adherent subjects, BMD also increased significantly ($p<0.001$) compared to baseline or placebo at both the hip and the spine in women assigned to Premarin or continuous Premarin/MPA. Spinal BMD increased 5.16% among women assigned to Premarin, increased 5.49% in women assigned to Premarin/MPA and decreased 2.82% in women assigned to placebo. At the hip, women assigned to Premarin gained 2.60%, women assigned to Premarin/MPA gained 2.23% while women assigned to placebo lost 2.17%.

These results are summarized in Tables 3 and 4 below.

Table 3. MEAN PERCENTAGE CHANGE FROM BASELINE IN BMD AT 36 MONTHS IN INTENT-TO-TREAT SUBJECTS**

	Spine			Hip		
Regimen	n	Mean % Change	95% CI	n	Mean % Change	95% CI
Premarin 0.625 mg	175	+3.46%*†	2.78, 4.14	175	+1.31%*†	0.76, 1.86
Premarin 0.625 mg/ MPA 2.5 mg	174	+4.87%*†	4.21, 5.52	174	+1.94%*†	1.50, 2.39
Placebo	174	-1.81%*	-2.51, -1.12	173	-1.62%*	-2.16, -1.08

* denotes a statistically significant mean change from baseline at the 0.001 level.
† denotes mean percentage change from baseline is significantly different from placebo at the 0.001 level.
** includes all 523 women who were randomized to either Premarin, Premarin/MPA or placebo whether or not they completed the study. If BMD was not available at 36 months, then the 12 months value was carried forward and analyzed. Baseline values were carried forward if 12 months and 36 months data were unavailable. Most patients who discontinued study medication were followed through month 36 and could have been off therapy for an extended period prior to their month 36 evaluation.

Table 4. MEAN PERCENTAGE CHANGE FROM BASELINE IN BMD AT 36 MONTHS IN ADHERENT SUBJECTS**

	Spine			Hip		
Regimen	n	Mean % Change	95% CI	n	Mean % Change	95% CI
Premarin 0.625 mg	95	+5.16%*†	4.32, 6.00	95	+2.60%*†	1.97, 3.23
Premarin 0.625 mg/ MPA 2.5 mg	144	+5.49%*†	4.79, 6.18	144	+2.23%*†	1.75, 2.71
Placebo	124	-2.82%*	-3.54, -2.10	123	-2.17%*	-2.78, -1.56

* denotes a statistically significant mean change from baseline at the 0.001 level.
† denotes mean percentage change from baseline is significantly different from placebo at the 0.001 level.
** women who completed the study had BMD reported at month 36, and took 80% or more of their prescribed study medication.

In general, older women (55-64 years of age) taking placebo in the PEPI study lost bone at a lower rate than younger women (45-54 years of age). Conversely, older women receiving Premarin or Premarin 0.625 mg/MPA 2.5 mg had greater increases in BMD than younger women. Tables 5 and 6 present data for women 45 to 54 years of age and women 55 to 64 years of age.

Table 5. MEAN PERCENTAGE CHANGE FROM BASELINE IN BMD FOR WOMEN 45 TO 54 YEARS OF AGE

	Intent-To-Treat Subjects				Adherent Subjects			
Regimen	n	Mean % Change at the Spine	n	Mean % Change at the Hip	n	Mean % Change at the Spine	n	Mean % Change at the Hip
Premarin 0.625 mg	74	+2.45%†**	74	+1.37%†**	43	+3.73%†**	43	+2.20%†**
Premarin 0.625 mg/ MPA 2.5 mg	69	+3.53%†**	69	+1.26%†**	58	+3.97%†**	58	+1.48%†**
Placebo	78	-2.82%**	78	-2.23%**	50	-4.02%**	50	-3.04%**

** denotes a statistically significant mean change from baseline at the 0.001 level.
† denotes mean percentage change from baseline is significantly different from placebo at the 0.001 level.

Table 6. MEAN PERCENTAGE CHANGE FROM BASELINE IN BMD FOR WOMEN 55 TO 64 YEARS OF AGE

	Intent-To-Treat Subjects				Adherent Subjects			
Regimen	n	Mean % Change at the Spine	n	Mean % Change at the Hip	n	Mean % Change at the Spine	n	Mean % Change at the Hip
Premarin 0.625 mg	101	+4.21%†‡**	101	+1.27%†**	52	+6.34%†‡**	52	+2.93%†**
Premarin 0.625 mg/ MPA 2.5 mg	105	+5.75%†‡**	105	+2.39%†**	86	+6.51%†‡**	86	+2.73%†**
Placebo	95	-1.01%*	94	-1.14%*	73	-2.04%‡**	72	-1.60%**

* denotes a statistically significant mean change from baseline at the 0.05 level.
** denotes a statistically significant mean change from baseline at the 0.001 level.
† denotes mean percentage change from baseline is significantly different from placebo at the 0.001 level.
‡ denotes mean percentage change from baseline in the older age group is significantly different from the mean percentage change in the younger age group at the 0.05 level.

Women's Health Initiative Studies.

A subset of the Women's Health Initiative (WHI) enrolled 16,608 predominantly healthy postmenopausal women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic) to assess the risks and benefits of long-term use of PREMPRO (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of PREMPRO on menopausal symptoms. The PREMPRO subset was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified long-term benefits included in the "global index". Results are presented in Table 7 below:

Table 7. RELATIVE AND ABSOLUTE RISK SEEN IN THE PREMPRO SUBSET OF WHI[a]

Event[c]	Relative Risk PREMPRO vs placebo at 5.2 Years (95% CI*)	Placebo n = 8102	PREMPRO n = 8506
		Absolute Risk per 10,000 Person-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index [c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis [d]	2.07 (1.49-2.87)	13	26
Vertebral fractures [d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures [d]	0.77 (0.69-0.86)	170	131

[a] adapted from JAMA, 2002; 288:321-333

[b] includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

[c] a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

[d] not included in Global Index

[*] nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

For those outcomes included in the "global index", absolute excess risks per 10,000 person-years in the group treated with PREMPRO were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 person-years. There was no difference between the groups in terms of all-cause mortality. (See **WARNINGS** and **PRECAUTIONS**.)

INDICATIONS AND USAGE

PREMPRO or PREMPHASE therapy is indicated in women with an intact uterus for the:

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

2. Treatment of vulvar and vaginal atrophy.

3. Prevention of postmenopausal osteoporosis.

PREMPRO and PREMPHASE are not indicated and should not be used to prevent coronary heart disease (see WARNINGS).

Because of the potential increased risks of cardiovascular events, breast cancer and venous thromboembolic events, use of PREMPRO or PREMPHASE should be limited to the shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically reevaluated. When used solely for the prevention of postmenopausal osteoporosis, alternative treatments should be carefully considered. (See WARNINGS and CLINICAL PHARMACOLOGY, Clinical Studies.)

Postmenopausal estrogen therapy reduces bone resorption and retards postmenopausal bone loss. Case-control studies have shown an approximately 60% reduction in hip and wrist fractures in women whose estrogen therapy was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen may prevent further loss of bone mass for as long as the treatment is continued. When estrogen therapy is discontinued, bone mass declines at a rate comparable to that of the immediate postmenopausal period.

The mainstays of prevention of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. The average calcium intake in the USA is 400-600 mg/day. 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.

Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton that are associated with osteoporosis include genetic factors (small build, family history), endocrine factors (nulliparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, type I diabetes), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight, dietary calcium intake).

CONTRAINDICATIONS

Estrogens/progestins combined should not be used in women under any of the following conditions or circumstances:

1. Known or suspected pregnancy. Estrogen or progestin may cause fetal harm when administered to a pregnant woman. (See **PRECAUTIONS**.)

2. Undiagnosed abnormal genital bleeding.

3. Known or suspected cancer of the breast.

4. Known or suspected estrogen-dependent neoplasia.

5. Active deep vein thrombosis/pulmonary embolism or a history of these conditions.

6. Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction).

7. Liver dysfunction or disease.

8. PREMPRO or PREMPHASE therapy should not be used in patients hypersensitive to the ingredients contained in the tablets.

WARNINGS

In a subset of the Women's Health Initiative study, PREMPRO was reported to increase the risks of cardiovascular events, breast cancer and venous thromboembolic events (see CLINICAL PHARMACOLOGY, Clinical Studies). Therefore, the use of postmenopausal estrogen/progestin therapy, including PREMPRO and PREMPHASE, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically reevaluated. When used solely for the prevention of postmenopausal osteoporosis, alternative treatments should be carefully considered.

1. **Cardiovascular disorders.**

Postmenopausal estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE).

Should any of these occur or be suspected, estrogen / progestin therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

a. Coronary heart disease and stroke. In the PREMPRO subset of the Women's Health Initiative study (WHI), an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving PREMPRO compared to women receiving placebo (37 vs 30 per 10,000 person-years). The increase in risk was observed in year one and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

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

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with PREMPRO (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with PREMPRO did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the PREMPRO-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the PREMPRO group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the

prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE). In the PREMPRO subset of WHI a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving PREMPRO compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the PREMPRO group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

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. Breast cancer. Long-term postmenopausal estrogen/progestin therapy has been associated with an increased risk of breast cancer.

In the PREMPRO subset of the Women's Health Initiative study, a 26% increase of invasive breast cancer (38 vs 30 per 10,000 woman-years) after an average of 5.2 years of treatment was observed in women receiving PREMPRO compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on PREMPRO. The women reporting prior postmenopausal hormone use had a higher relative risk for breast cancer associated with PREMPRO than those who had never used postmenopausal hormones. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

A reanalysis of original data from 51 epidemiological studies (not necessarily including PREMPRO or PREMPHASE) reported an increase in the probability of having breast cancer diagnosed in women currently or recently using postmenopausal hormone (estrogen and/or estrogen/progestin) therapy. The authors estimate that among 1,000 women who begin hormone therapy at age 50 and continue for 5 years, 10 years or 15 years, the additional number of cases of breast cancer that would occur by age 70 would be 2 cases, 6 cases and 12 cases, respectively. The probability of a diagnosis of breast cancer approached normal by five years after stopping postmenopausal hormone therapy. Additional epidemiological studies suggest that the addition of progestins increases the risk of breast cancer compared to the use of estrogens alone.

Women without a uterus who require postmenopausal hormone therapy should receive estrogen-alone therapy and should not be exposed unnecessarily to progestins. Women with a uterus who are candidates for use of postmenopausal estrogen/progestin therapy should be advised of potential benefits and risks (including the potential for an increased risk of breast cancer). All women should receive yearly breast exams by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.

b. Endometrial cancer. The reported endometrial cancer risk among users of unopposed estrogen was about 2- to 12-fold greater than in nonusers 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 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

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

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported in a large clinical trial to occur at a rate of approximately 1% or less with PREMPRO or PREMPHASE. In this large clinical trial, only a single case of endometrial cancer was reported to occur among women taking combination Premarin/medroxyprogesterone acetate therapy.

c. Ovarian cancer. The association between postmenopausal estrogen therapy and ovarian cancer was evaluated in several case-control and cohort studies. Two large cohort studies suggested an increased risk of ovarian cancer associated with long-term postmenopausal estrogen-only therapy, particularly for 10 or more years of use. In one of these studies, the baseline incidence among untreated postmenopausal women was reported to be 4.4 cases per 10,000 woman-years, compared to 6.5 cases per 10,000 woman-years among women using postmenopausal estrogen therapy. Other epidemiologic studies of postmenopausal estrogen therapy and ovarian cancer did not show a significant association. Data are insufficient to determine whether there is an increased risk with postmenopausal estrogen/progestin therapy.

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

4. **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.

5. **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, PREMPRO or PREMPHASE 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 in postmenopausal hormone therapy regimens compared to estrogen-alone regimens. These include an increased risk of breast cancer (see **WARNINGS**, **Malignant neoplasms**), adverse effects on lipoprotein metabolism (eg, 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 during postmenopausal estrogen therapy have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

*3. **Familial hyperlipoproteinemia.***

In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

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

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

*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/progestins 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. **Exacerbation of endometriosis.***

Endometriosis may be exacerbated with administration of estrogen therapy.

*9. **Exacerbation of other conditions.***
Postmenopausal estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria and should be used with caution in women with these conditions.

B. Patient Information
See text of Patient Information insert after the **HOW SUPPLIED** section.

C. Laboratory Tests
Estrogen administration should generally be guided by clinical response at the lowest dose for the treatment of vasomotor symptoms and vulvar and vaginal atrophy.

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 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) leading to increased circulating total thyroid hormone, 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.

3. Other binding proteins may be elevated in serum, ie, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. 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 concentration, increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

8. Aminoglutethimide administered concomitantly with medroxyprogesterone acetate (MPA) may significantly depress the bioavailability of MPA.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breasts, uterus, cervix, vagina, testis, and liver. (See **CONTRAINDICATIONS** and **WARNINGS**.)

In a two-year oral study of medroxyprogesterone acetate (MPA) in which female rats were exposed to dosages of up to 5000 μg/kg/day in their diets (50 times higher – based on AUC values – than the level observed experimentally in women taking 10 mg of MPA), a dose-related increase in pancreatic islet cell tumors (adenomas and carcinomas) occurred. Pancreatic tumor incidence was increased at 1000 and 5000 μg/kg/day, but not at 200 μg/kg/day.

A decreased incidence of spontaneous mammary gland tumors was observed in all three MPA-treated groups, compared to controls, in the two-year rat study. The mechanism for the decreased incidence of mammary gland tumors observed in the MPA-treated rats may be linked to the significant decrease in serum prolactin concentration observed in rats.

Beagle dogs treated with MPA developed mammary nodules, some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. It is known that progestogens stimulate synthesis and release of growth hormone in dogs. The growth hormone, along with the progestogen, stimulates mammary growth and tumors. In contrast, growth hormone in humans is not increased, nor does growth hormone have any significant mammotrophic role. No pancreatic tumors occurred in dogs.

F. Pregnancy Category X
PREMPRO and PREMPHASE should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

G. Nursing Mothers
The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. The effect of this on the nursing infant has not been determined. PREMPRO and PREMPHASE are not indicated for the prevention of postpartum breast engorgement.

H. Pediatric Use
PREMPRO and PREMPHASE are not indicated in children.

I. Geriatric Use
There have not been sufficient numbers of geriatric patients involved in studies utilizing Premarin and medroxyprogesterone acetate to determine whether those over 65 years of age differ from younger subjects in their response to PREMPRO or PREMPHASE.

ADVERSE REACTIONS
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.

See **WARNINGS** regarding cardiovascular disorders (including myocardial infarction, stroke and venous thromboembolism), malignant neoplasms (including breast cancer, endometrial cancer and ovarian cancer), gallbladder disease, hypercalcemia and visual abnormalities. See **PRECAUTIONS** regarding elevated blood pressure, familial hyperlipoproteinemia, impaired liver function and past history of cholestatic jaundice, hypothyroidism, fluid retention, hypocalcemia, exacerbation of endometriosis and other conditions.

In a one-year clinical trial that included 678 women treated with PREMPRO, 351 women treated with PREMPHASE, and 347 women treated with Premarin, the following adverse events occurred at a rate ≥5% (see Table 8):

Table 8. ALL TREATMENT EMERGENT STUDY EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY ³ 5%

	PREMPRO 0.625 mg/2.5 mg continuous (n=340)	PREMPRO 0.625 mg/5.0 mg continuous (n=338)	PREMPHASE 0.625 mg/5.0 mg sequential (n=351)	PREMARIN 0.625 mg daily (n=347)
Body as a whole				
abdominal pain	16%	21%	23%	17%
accidental injury	5%	4%	5%	5%
asthenia	6%	8%	10%	8%
back pain	14%	13%	16%	14%
flu syndrome	10%	13%	12%	14%
headache	36%	28%	37%	38%
infection	16%	16%	18%	14%
pain	11%	13%	12%	13%
pelvic pain	4%	5%	5%	5%
Digestive system				
diarrhea	6%	6%	5%	10%
dyspepsia	6%	6%	5%	5%
flatulence	8%	9%	8%	5%
nausea	11%	9%	11%	11%
Metabolic and Nutritional				
peripheral edema	4%	4%	3%	5%
Musculoskeletal system				
arthralgia	9%	7%	9%	7%
leg cramps	3%	4%	5%	4%
Nervous system				
depression	6%	11%	11%	10%
dizziness	5%	3%	4%	6%
hypertonia	4%	3%	3%	7%
Respiratory system				
pharyngitis	11%	11%	13%	12%
rhinitis	8%	6%	8%	7%
sinusitis	8%	7%	7%	5%
Skin and appendages				
pruritus	10%	8%	5%	4%
rash	4%	6%	4%	3%
Urogenital system				
breast pain	33%	38%	32%	12%
cervix disorder	4%	4%	5%	5%
dysmenorrhea	8%	5%	13%	5%
leukorrhea	6%	5%	9%	8%
vaginal hemorrhage	2%	1%	3%	6%
vaginitis	7%	7%	5%	3%

The following adverse reactions also 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, change in amount of cervical secretion, premenstrual-like syndrome, cystitis-like syndrome, increase in size of uterine leiomyomata, vaginal candidiasis, amenorrhea, changes in cervical erosion, ovarian cancer.

2. *Breasts*
Tenderness, enlargement, galactorrhea, discharge, fibrocystic breast changes.

3. *Gastrointestinal*
Nausea, cholestatic jaundice, changes in appetite, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease, pancreatitis.

4. *Skin*
Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, urticaria, pruritus, generalized rash, rash (allergic) with and without pruritus, acne.

5. *Cardiovascular*
Change in blood pressure, deep and superficial venous thrombosis/thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and embolism.

6. *CNS*
Headache, dizziness, mental depression, mood disturbances, anxiety, irritability, nervousness, migraine, chorea, insomnia, somnolence.

7. *Eyes*
Neuro-ocular lesions, eg, retinal thrombosis and optic neuritis, steepening of corneal curvature, intolerance of contact lenses.

8. *Miscellaneous*
Increase or decrease in weight, edema, changes in libido, fatigue, backache, reduced carbohydrate tolerance, aggravation of porphyria, pyrexia, anaphylactoid/anaphylactic reactions including urticaria and angioedema .

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

DOSAGE AND ADMINISTRATION
Use of postmenopausal estrogen/progestin therapy should be limited to the shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically reevaluated. (See **WARNINGS**.)

PREMPRO therapy consists of a single tablet to be taken once daily.

1. For treatment of moderate-to-severe vasomotor symptoms and/or vulvar and vaginal atrophy associated with the menopause, patients should be started at the lowest effective dose – PREMPRO 0.625 mg/2.5 mg daily. Patients should be reevaluated at 3-month to 6-month intervals to determine if treatment for symptoms is still necessary.

   Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal

vaginal bleeding. In patients where bleeding or spotting remains a problem, after appropriate evaluation, consideration should be given to increasing the medroxyprogesterone acetate (MPA) dose to PREMPRO 0.625 mg/5 mg daily. This dose should be periodically reassessed by the healthcare provider.

2. For prevention of postmenopausal osteoporosis – PREMPRO 0.625 mg/2.5 mg daily. When used solely for the prevention of postmenopausal osteoporosis, alternative treatments should be carefully considered. In patients where bleeding or spotting remains a problem, after appropriate evaluation, consideration should be given to increasing the MPA dose to PREMPRO 0.625 mg/5 mg daily. This dose should be periodically reassessed by the healthcare provider.

Patients should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMPHASE therapy consists of two separate tablets; one maroon 0.625 mg Premarin tablet taken daily on days 1 through 14 and one light-blue tablet, containing 0.625 mg conjugated estrogens and 5 mg of medroxyprogesterone acetate, taken on days 15 through 28.

1. For treatment of moderate to severe vasomotor symptoms and/or vulvar and vaginal atrophy associated with the menopause. Patients should be reevaluated at 3-month to 6-month intervals to determine if treatment for symptoms is still necessary. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

2. For prevention of postmenopausal osteoporosis. When PREMPHASE is used solely for the prevention of postmenopausal osteoporosis, alternative treatments should be carefully considered.

Patients should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

PREMPRO™ therapy consists of a single tablet to be taken once daily.

PREMPRO 0.625 mg/2.5 mg

Each carton includes 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, peach tablets containing 0.625 mg of the conjugated estrogens found in Premarin® tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/5 mg

Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, light-blue tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

PREMPHASE® therapy consists of two separate tablets; one maroon Premarin tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28.

Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 14 oval, maroon Premarin® tablets containing 0.625 mg of conjugated estrogens and 14 oval, light-blue tablets that contain 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

The appearance of PREMPRO tablets is a trademark of Wyeth-Ayerst Laboratories.

The appearance of Premarin tablets is a trademark of Wyeth-Ayerst Laboratories. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a registered trademark.

Store at controlled room temperature 20°C - 25°C (68°F - 77°F).

PATIENT INFORMATION

This leaflet summarizes the major risks and benefits of treatment with PREMPRO or PREMPHASE. Read this PATIENT INFORMATION before using the product and each time you get medicine because there may be new information. Talk with your healthcare provider if you have any questions about this medicine.

What is PREMPRO or PREMPHASE?

PREMPRO or PREMPHASE is a combination of two hormones, an estrogen and a progestin.

What is PREMPRO or PREMPHASE used for?

The use of PREMPRO or PREMPHASE may increase your risk of getting breast cancer, blood clots, heart attacks, and strokes. PREMPRO and PREMPHASE should be used only as long as needed. Periodically, you and your healthcare provider should discuss whether you still need treatment.

PREMPRO and PREMPHASE should not be used to prevent heart disease.

PREMPRO and PREMPHASE are used

- **To reduce moderate to severe menopausal symptoms.**
  Estrogens are hormones produced by a woman's ovaries. Between the ages of 45 and 55, the ovaries normally stop making estrogens. This drop in body estrogen level 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 develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild; in others they can be severe. Taking PREMPRO or PREMPHASE can help reduce these symptoms.

  Every 3 to 6 months you and your healthcare provider should discuss whether you still need PREMPRO or PREMPHASE to control your hot flushes.

- **To treat itching, burning, and dryness in and around the vagina due to menopause.**
  Every 3 to 6 months you and your healthcare provider should discuss whether you still need PREMPRO or PREMPHASE to control your vaginal symptoms.

- **To help reduce your chance of getting osteoporosis (thin weak bones).**
  Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily.

  If you use PREMPRO or PREMPHASE only to prevent osteoporosis, discuss with your healthcare provider whether a different treatment might be more appropriate for you.

Women who have menopause at an early age, are thin, smoke and/or have a family history of osteoporosis are more likely to develop osteoporosis.

PREMPRO or PREMPHASE may be used as part of a program which includes weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements to reduce your chances of getting osteoporosis. Before you change your exercise habits or calcium or vitamin D intake, it is important to discuss these lifestyle changes with your healthcare provider to find out if they are safe for you. Before you make any change in your use of PREMPRO or PREMPHASE, talk with your healthcare provider.

During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for this.

Who should not take PREMPRO or PREMPHASE?

Do not take PREMPRO or PREMPHASE

- **If you think you may be pregnant.**
  Taking PREMPRO or PREMPHASE while you are pregnant may harm your unborn child. Do not take PREMPRO or PREMPHASE to prevent miscarriage.

- **If you have unusual vaginal bleeding.**
  Unusual vaginal bleeding can be a warning sign of a serious condition, including cancer of the uterus, especially if it happens after menopause. If you develop vaginal bleeding while taking PREMPRO or PREMPHASE, you may need further evaluation. Your healthcare provider needs to find out the cause of the bleeding so you can receive proper treatment. If you develop vaginal bleeding while taking PREMPRO or PREMPHASE talk with your healthcare provider about proper treatment.

- **If you have or had certain cancers.**
  Estrogens may increase the risk of certain types of cancer, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should take PREMPRO or PREMPHASE.

- **If you have or had blood clots, a heart attack, or a stroke.**
  Talk with your healthcare provider if you have or had these conditions, or if you have abnormal blood clotting conditions.

- **If you have recently had a baby.**
  PREMPRO and PREMPHASE can be passed to the nursing baby in the breastmilk. The effect of this on the baby is not known. Do not take PREMPRO or PREMPHASE to stop your breasts from filling with milk after a baby is born.

- **If you had your uterus removed.**
  PREMPRO or PREMPHASE contain a progestin to decrease the risk of developing endometrial hyperplasia (an overgrowth of the lining of the uterus that may lead to cancer).

In general, if you do not have a uterus, you do not need a progestin, and you should not take PREMPRO or PREMPHASE.

- **If you have liver problems.**
  Talk with your healthcare provider about your condition.

- **If you are allergic to PREMPRO or PREMPHASE or any of their ingredients.**

How should I take PREMPRO or PREMPHASE?

- Take 1 PREMPRO or PREMPHASE tablet each day at the same time.

- If you miss a dose, take it as soon as possible. However, 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.

PREMPRO comes in two strengths. Check with your healthcare provider periodically to make sure you are using the appropriate dose.

PREMPRO or PREMPHASE use may increase your risk of getting breast cancer, blood clots, heart attacks, and strokes. PREMPRO and PREMPHASE should be used only as long as needed. Periodically, you and your healthcare provider should discuss whether you still need treatment.

What are the possible risks and side effects of PREMPRO or PREMPHASE?

1. **Heart disease, stroke and blood clots**
   The use of PREMPRO or PREMPHASE may increase your chance of having a heart attack, a stroke, blood clots, a pulmonary embolus (a blood clot formed in the legs or pelvis that breaks off and travels to the lungs), retinal thrombosis (a clot in a blood vessel of the eye), or other blood clotting problems. Any of these conditions may cause death or serious long-term disability. These conditions have been seen in healthy, postmenopausal women, as well as in women with a history of heart disease.

2. **Cancer of the breast**
   Long-term use of PREMPRO or PREMPHASE may increase your chance of having breast cancer. Regular breast exams by a health professional and monthly self-exams are recommended for all women. Mammography should be scheduled depending on your age and risk factors.

3. **Cancer of the uterus**
   Estrogens increase the risk of getting a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. The risk of cancer of the uterus increases when estrogens are used alone, the longer they are used, and when larger doses are taken. Taking progestins with estrogens lowers the risk of getting this condition. PREMPRO and PREMPHASE contain estrogen and progestin.

4. **Ovarian cancer**
   Some studies suggest that there is a greater risk of ovarian cancer in women who have used estrogen alone for a long period of time, especially 10 years or more. Other studies have not shown this risk. The risk with PREMPRO or PREMPHASE treatment is unclear.

5. **Vaginal bleeding**
   If you develop vaginal bleeding while taking PREMPRO or PREMPHASE, discuss your bleeding pattern with your healthcare provider. This is because vaginal bleeding after menopause may be a warning sign of a serious condition, including cancer of the uterus.

6. **Gallbladder disease**
   Women who use PREMPRO or PREMPHASE after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

7. **Blood pressure**
   Some women who are taking PREMPRO or PREMPHASE may have increases in blood pressure.

8. **Liver problems**
   If you had yellowing of your skin or eyes associated with pregnancy, or with taking estrogens (eg, oral contraceptives), this condition may occur again with PREMPRO or PREMPHASE treatment.

9. **Hypothyroidism**
   Women who are taking PREMPRO or PREMPHASE, and who use thyroid replacement therapy may require increased doses of their thyroid medication.

10. **Effects on blood sugar**
    Taking PREMPRO or PREMPHASE may affect blood sugar levels, which might make a diabetic condition worse.

11. **Other conditions**
    Fluid retention due to PREMPRO or PREMPHASE treatment may make some conditions worse, such as heart disease or kidney disease. Estrogen treatment may also worsen asthma, epilepsy, migraine, porphyria and endometriosis.

In addition to the risks listed above, the following common side effects have been reported with estrogen and/or progestin use:

- Nausea, vomiting, pain, cramps, swelling, or tenderness in the abdomen.
- Breast tenderness or enlargement, pain or discharge.
- Enlargement of benign tumors ("fibroids") of the uterus.
- Change in amount of cervical secretion.
- Vaginal yeast infections.

- A spotty darkening of the skin, particularly on the face; reddening of the skin; skin rashes.
- Retention of fluid (edema).
- Headache, migraines, dizziness, or changes in vision (including intolerance to contact lenses).
- Mental depression.
- Involuntary muscle spasms.
- Hair loss or abnormal hairiness.
- Increase or decrease in weight.
- Changes in sex drive.

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

If you take PREMPRO or PREMPHASE you can reduce your risks by doing these things:

· **See your healthcare provider regularly.**

Check with your healthcare provider to make sure you do not stay on treatment longer than needed. While you are taking PREMPRO or PREMPHASE, it is important to visit your healthcare provider at least once a year for a checkup. If you develop vaginal bleeding while taking PREMPRO or PREMPHASE, you may need further evaluation. Every 3 to 6 months you and your healthcare provider should discuss whether or not you still need PREMPRO or PREMPHASE to control your hot flushes and vaginal symptoms.

You should talk with your healthcare provider about stopping PREMPRO or PREMPHASE 4 to 6 weeks before surgery or during prolonged bedrest.

If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast X-ray), you may need to have more frequent breast examinations. Examine your breasts for changes every month.

· **Be alert to signs of trouble.**

If any of the following warning signals (or any other unusual symptoms) happen while you are using PREMPRO or PREMPHASE, call your healthcare provider immediately:

- Abnormal bleeding from the vagina (possible uterine abnormality/cancer).
- Pains in the calves or chest, a sudden shortness of breath or coughing blood (indicating possible clots in the legs, heart, or lungs).

- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (indicating possible clots in the brain [stroke] or eye).

- Breast lumps (possible breast cancer). Ask your healthcare provider to show you how to examine your breasts.

- Yellowing of the skin and/or whites of the eyes (possible liver problems).

- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem).

Other information

1. Your healthcare provider prescribed this drug for you and you alone. Do not give this drug to anyone else.

2. Keep this and all drugs out of reach of children. In case of overdose, call your doctor or healthcare provider, hospital, or poison control center right away.

HOW SUPPLIED
PREMPRO™ therapy consists of a single tablet to be taken once daily.

PREMPRO 0.625 mg/2.5 mg
Each carton includes 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, peach tablets containing 0.625 mg of the conjugated estrogens found in Premarin® tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, light-blue tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

PREMPHASE® therapy consists of two separate tablets; one maroon Premarin tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28.

Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 14 oval, maroon Premarin tablets containing 0.625 mg of conjugated estrogens and 14 oval, light-blue tablets that contain 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

The appearance of PREMPRO tablets is a trademark of Wyeth-Ayerst Laboratories.

The appearance of Premarin tablets is a trademark of Wyeth-Ayerst Laboratories. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a registered trademark.

Keep out of reach of children.

Store at controlled room temperature 20°C - 25°C (68°F - 77°F).

U.S. Patent Nos. 5,547,948; 5,210,081; Re. 36,247

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