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

Rx only

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**). Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens and progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

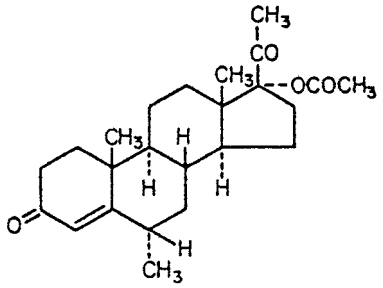
DESCRIPTION

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, FD&C Yellow No. 6. 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 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 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.

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)

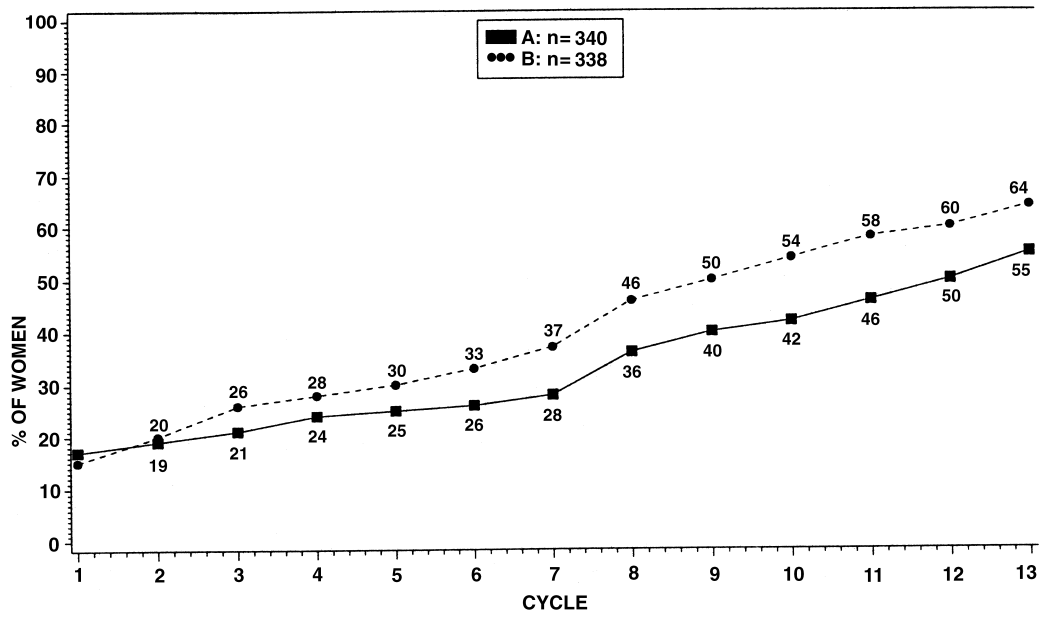
*Significant ($p < 0.001$) in comparison with Premarin (0.625 mg) alone.

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.

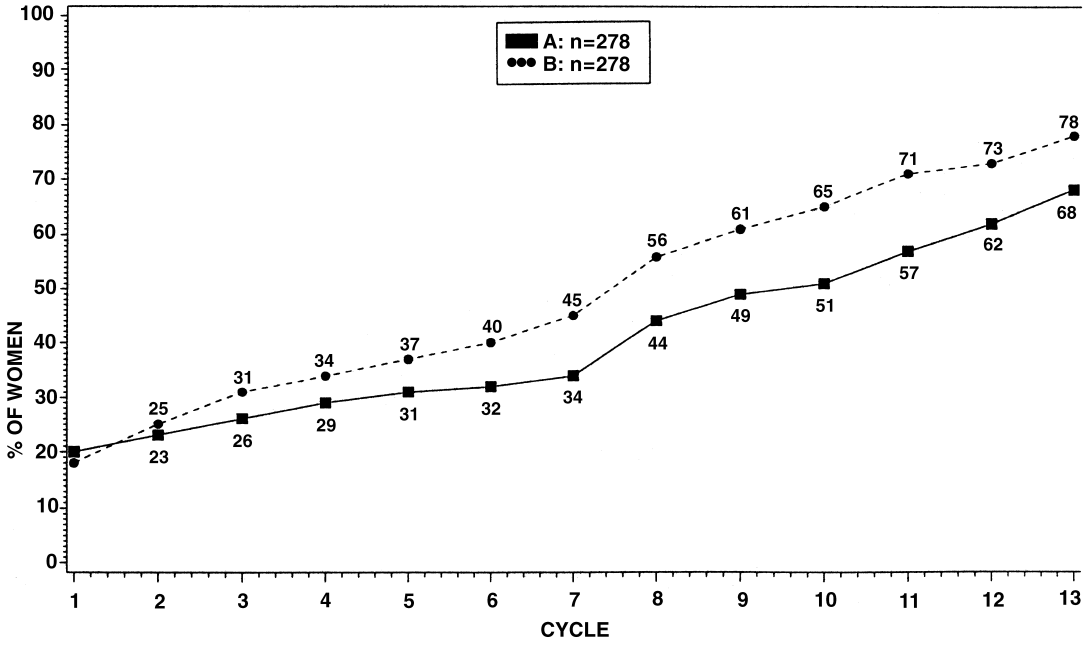
Figure 1. Patients with Cumulative Amenorrhea Over Time

(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 substudy 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 the 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 substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results are presented in Table 7 below:

Table 7. RELATIVE AND ABSOLUTE RISK SEEN IN THE PREMPRO SUBSTUDY 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 **BOXED WARNING, WARNINGS** and **PRECAUTIONS**.)

INDICATIONS AND USAGE

PREMPRO or PREMPHASE therapy is indicated in women who have a uterus for 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. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

   The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/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/progestins combined should not be used in women under any of the following conditions:

1. Undiagnosed abnormal genital bleeding.

2. Known, suspected, or history of cancer of the breast.

3. Known or suspected estrogen-dependent neoplasia.

4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.

5. Active or recent (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).

6. Liver dysfunction or disease.

7. PREMPRO or PREMPHASE therapy should not be used in patients with known hypersensitivity to their ingredients.

8. Known or suspected pregnancy. There is no indication for PREMPRO or PREMPHASE in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogen and progestins from oral contraceptives inadvertently during pregnancy. (See **PRECAUTIONS**.)

WARNINGS
See **BOXED WARNING.**

1. **Cardiovascular disorders.**

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.

Risk factors for cardiovascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) should be managed appropriately.

a. Coronary heart disease and stroke. In the PREMPRO substudy 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 substudy 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 substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving PREMPRO compared to women receiving placebo. The rate of VTE was 34 per 10,000 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. Estrogen/progestin therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the PREMPRO substudy 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 use of estrogen and/or estrogen with progestin had a higher relative risk for breast cancer associated with PREMPRO than those who had never used these hormones. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens, with or without progestin. This association was reanalyzed in original data from 51 studies that involved treatment with various doses and types of estrogens, with and without progestin. In the reanalysis, an increased risk of having breast cancer diagnosed became apparent after about 5 years of continued treatment, and subsided after treatment had been discontinued for about 5 years. Some later studies have suggested that treatment with estrogen and progestin increases the risk of breast cancer more than treatment with estrogen alone.

A postmenopausal woman without a uterus who requires estrogen should receive estrogen-alone therapy and should not be exposed unnecessarily to progestins. All postmenopausal women should receive yearly breast exams by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled 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.

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, estrogens should be discontinued.

PRECAUTIONS

A. General

1. ***Addition of a progestin when a woman has not had a hysterectomy.***
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

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

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

3. ***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. ***Ovarian cancer.***
Use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with combined estrogen/progestin therapy in postmenopausal women.

9. ***Exacerbation of endometriosis.***
Endometriosis may be exacerbated with administration of estrogens.

10. ***Exacerbation of other conditions.***
Estrogens 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
Physicians are advised to discuss the contents of the PATIENT INFORMATION leaflet with patients for whom they prescribe PREMPRO or PREMPHASE.

C. Laboratory Tests
Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).

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) 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 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. 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 **BOXED WARNING, 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 mcg/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 mcg/kg/day, but not at 200 mcg/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

PREMPRO and PREMPHASE 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 estrogen and progestin have been identified in the milk of mothers receiving these drugs. Caution should be exercised when PREMPRO or PREMPHASE are administered to a nursing woman.

H. Pediatric Use

PREMPRO and PREMPHASE are not indicated in children.

I. Geriatric Use

Of the total number of subjects in the PREMPRO substudy of the Women's Health Initiative study, 44% (n=7320) were 65 years and over, while 6.6% (n=1,095) were 75 and over (see **CLINICAL PHARMACOLOGY, Clinical Studies**). No significant differences in safety were observed between subjects 65 years and over compared to younger subjects. There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to younger subjects.

With respect to efficacy in the approved indications, 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

See **BOXED WARNING, 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.

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 ≥ 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%

	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)
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, endometrial hyperplasia, endometrial cancer.

2. *Breasts*
Tenderness, enlargement, galactorrhea, discharge, 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, cholestatic jaundice, changes in appetite, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease, pancreatitis.

5. *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.

6. *Eyes*
Neuro-ocular lesions, e.g., retinal vascular thrombosis and optic neuritis, steepening of corneal curvature, intolerance of contact lenses.

7. *CNS*
Headache, dizziness, mental depression, mood disturbances, anxiety, irritability, nervousness, migraine, chorea, insomnia, somnolence, exacerbation of epilepsy.

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, hypocalcemia, exacerbation of asthma, increased triglycerides.

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

PREMPRO therapy consists of a single tablet to be taken once daily. Patients should be started at the lowest available dose.

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.

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.

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

<u>PREMPRO 0.625 mg/2.5 mg</u>
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 Pharmaceuticals.

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

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

PATIENT INFORMATION
(Updated January 3, 2003)

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

Read this PATIENT INFORMATION before you start taking PREMPRO or PREMPHASE and read what you get each time you refill PREMPRO or PREMPHASE. 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 PREMPRO and PREMPHASE (combinations of estrogens and a progestin)?

Do not use estrogens and progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens and progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots. You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE.

What is PREMPRO or PREMPHASE?

PREMPRO or PREMPHASE are medicines that contain two kinds of hormones, estrogens and a progestin.

PREMPRO or PREMPHASE 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 to 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 there is no 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 PREMPRO or PREMPHASE.

- **treat moderate to severe dryness, itching, and burning, in and around your vagina**. You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE to control these problems.

- **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 PREMPRO or PREMPHASE 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 PREMPRO or PREMPHASE.

  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.

Who should not take PREMPRO or PREMPHASE?

Do not take PREMPRO or PREMPHASE if you have had your uterus removed (hysterectomy). PREMPRO and PREMPHASE contain a progestin to decrease the chances of getting cancer of the uterus. If you do not have a uterus, you do not need a progestin and you should not take PREMPRO or PREMPHASE.

Do not start taking PREMPRO or PREMPHASE if you:

- **have unusual vaginal bleeding.**

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

- **had a stroke or heart attack in the past year.**

- **currently have or have had clots.**

- **have liver problems.**

- **are allergic to PREMPRO or PREMPHASE or any of their ingredients.** See the end of this leaflet for a list of all the ingredients in PREMPRO and PREMPHASE.

- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breastfeeding.** The hormones in PREMPRO and PREMPHASE 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, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood**.**

- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PREMPRO or PREMPHASE works. PREMPRO or PREMPHASE 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 and progestins.

How should I take PREMPRO or PREMPHASE?

- Take one PREMPRO or PREMPHASE 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 only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about whether you still need treatment with PREMPRO or PREMPHASE.

What are the possible side effects of PREMPRO or PREMPHASE?

Less common but serious side effects include:
- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:
- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in Speech
- Severe headaches
- Chest Pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

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

Common side effects 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
- Mental depression

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

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

- Talk with your healthcare provider regularly about whether you should continue taking PREMPRO or PREMPHASE.
- See your healthcare provider right away if you get vaginal bleeding while taking PREMPRO or PREMPHASE.
- 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 PREMPRO and PREMPHASE

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take PREMPRO or PREMPHASE for conditions for which they were not prescribed. Do not give PREMPRO or PREMPHASE to other people, even if they have the same symptoms you have. It may harm them. **Keep PREMPRO and PREMPHASE out of the reach of children.**

This leaflet provides a summary of the most important information about PREMPRO and PREMPHASE. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about PREMPRO and PREMPHASE 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 PREMPRO and PREMPHASE?

PREMPRO contains 0.625 mg of the same conjugated estrogens found in Premarin® 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. PREMPRO also contains either 2.5 or 5 mg of medroxyprogesterone acetate. PREMPRO also contains calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, and red ferric oxide or FD&C Blue No. 2.

PREMPHASE is two separate tablets. One tablet (maroon color) is 0.625 mg of Premarin® which is 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. The maroon tablet also contains 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. The second tablet (light blue color) contains 0.625 mg of the same ingredients as the maroon color tablet plus 5 mg of medroxyprogesterone acetate. The light blue tablet also contains 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, and FD&C Yellow No. 6.

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

<u>PREMPRO 0.625 mg/2.5 mg</u>
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.

<u>PREMPRO 0.625 mg/5 mg</u>
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.

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

Ayerst Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101

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