

Premarin[®]

(conjugated estrogens tablets, USP)

R_{only}

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

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

CARDIOVASCULAR AND OTHER RISKS

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

DESCRIPTION

Premarin[®] (conjugated estrogens tablets, USP) for oral administration contains a mixture of conjugated equine estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares’ urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17 α -dihydroequilin, 17 α -estradiol, and 17 β -dihydroequilin. Tablets for oral administration are available in 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg strengths of conjugated estrogens.

Premarin Tablets contain 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.

—0.3 mg tablets also contain: D&C Yellow No. 10, FD&C Blue No. 1, FD&C Blue No. 2, FD&C Yellow No. 6; these tablets comply with USP Drug Release Test 1.

—0.625 mg tablets also contain: FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40; these tablets comply with USP Drug Release Test 1.

—0.9 mg tablets also contain: D&C Red No. 6, D&C Red No. 7; these tablets comply with USP Drug Release Test 2.

—1.25 mg tablets also contain: black iron oxide, D&C Yellow No. 10, FD&C Yellow No. 6; these tablets comply with USP Drug Release Test 3.

—2.5 mg tablets also contain: FD&C Blue No. 2, D&C Red No. 7; these tablets comply with USP Drug Release Test 3.

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 micrograms 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 estrogen in postmenopausal women.

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

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

Pharmacokinetics

Absorption

Conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. The Premarin tablet releases conjugated estrogens slowly over several hours. The pharmacokinetic profile of unconjugated and conjugated estrogens following a dose of 2 x 0.625 mg is provided in Table 1.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentration in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone-binding globulin (SHBG) and albumin.

Metabolism

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

Excretion

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

Table 1. PHARMACOKINETIC PARAMETERS FOR PREMARIN

Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 2 x 0.625 mg*

Drug	C _{max} (pg/mL)	t _{max} (h)	t _{1/2} ** (h)	AUC (pg•h/mL)
estrone	139 (37)	8.8 (20)	28.0 (13)	5016 (34)
baseline-adjusted estrone	120 (42)	8.8 (20)	17.4 (37)	2956 (39)
equilin	66 (42)	7.9 (19)	13.6 (52)	1210 (37)

*Mean (Coefficient of Variation, %)

** t_{1/2} = terminal-phase disposition half-life (0.693/γ₂)

Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 2 x 0.625 mg*

Drug	C _{max} (ng/mL)	t _{max} (h)	t _{1/2} ** (h)	AUC (ng•h/mL)
total estrone	7.3 (41)	7.3 (51)	15.0 (25)	134 (42)
baseline-adjusted total estrone	7.1 (41)	7.3 (25)	13.6 (27)	122 (39)
total equilin	5.0 (42)	6.2 (26)	10.1 (27)	65 (45)

*Mean (Coefficient of Variation, %)

** t_{1/2} = terminal-phase disposition half-life (0.693/γ₂)

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 dispositions of both drugs are not significantly altered. No other clinical drug-drug interaction studies have been conducted with conjugated estrogens.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Clinical Studies

Effects on 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, a regimen similar to Prempro™.

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 2 and 3 below.

Table 2. MEAN PERCENTAGE CHANGE FROM BASELINE IN BMD AT 36 MONTHS IN INTENT-TO-TREAT SUBJECTS**

Regimen	Spine			Hip		
	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 3. MEAN PERCENTAGE CHANGE FROM BASELINE IN BMD AT 36 MONTHS IN ADHERENT SUBJECTS**

Regimen	Spine			Hip		
	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 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 4 and 5 present data for women 45 to 54 years of age and women 55 to 64 years of age.

Table 4. MEAN PERCENTAGE CHANGE FROM BASELINE IN BMD FOR WOMEN 45 TO 54 YEARS OF AGE

Regimen	Intent-To-Treat Subjects				Adherent Subjects			
	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 5. MEAN PERCENTAGE CHANGE FROM BASELINE IN BMD FOR WOMEN 55 TO 64 YEARS OF AGE

Regimen	Intent-To-Treat Subjects				Adherent Subjects			
	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.

The Women’s Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of Premarin (0.625 mg conjugated equine estrogens per day) alone or 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 Premarin or Prempro on menopausal symptoms.

The Premarin-only substudy is continuing and results have not been reported. 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 of the Prempro substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 6 below:

Table 6. 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
<i>Non-fatal MI</i>	<i>1.32 (1.02-1.72)</i>	23	30
<i>CHD death</i>	<i>1.18 (0.70-1.97)</i>	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 WARNINGS, WARNINGS, and PRECAUTIONS.**)

INDICATIONS AND USAGE

Premarin therapy is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).
6. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and 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 should not be used in individuals with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
5. Active or recent (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Premarin Tablets should not be used in patients with known hypersensitivity to their ingredients.
7. Known or suspected pregnancy. There is no indication for Premarin in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogen and progestins from oral contraceptives inadvertently during pregnancy. (See **PRECAUTIONS.**)

WARNINGS

See **BOXED WARNINGS**.

The use of unopposed estrogens in women who have a uterus is associated with an increased risk of endometrial cancer.

1. **Cardiovascular disorders.**

Estrogen and estrogen/progestin therapy have 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, estrogens 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 Premarin substudy of the Women's Health Initiative (WHI), an increase in the number of myocardial infarctions and strokes has been observed in women receiving Premarin compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the Prempro substudy of 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.

In the same substudy of the 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 estrogen 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 risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE). In the Premarin substudy of the Women's Health Initiative (WHI), an increase in VTE has been observed in women receiving Premarin compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

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.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms.

a. Endometrial cancer. The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

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

b. Breast cancer. Estrogen and estrogen/progestin therapy in postmenopausal women have been associated with an increased risk of breast cancer. In the Prempro substudy of the Women's Health Initiative study (WHI), 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.**)

In the Premarin substudy of WHI, no increased risk of breast cancer in estrogen-treated women compared to placebo was reported after an average of 5.2 years of therapy. These data are preliminary and that substudy of WHI is continuing.

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.

3. Gallbladder disease.

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving postmenopausal 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 T₄ and T₃ serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention.

Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a 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 estrogen therapy.

10. Exacerbation of other conditions.

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria and should be used with caution in patients with these conditions.

B. Patient Information

Physicians are advised to discuss the contents of the PATIENT INFORMATION leaflet with patients for whom they prescribe Premarin.

C. Laboratory Tests

Estrogen administration should be guided by clinical response at the lowest dose for the treatment of postmenopausal moderate to severe vasomotor symptoms and moderate to severe symptoms of postmenopausal vulvar and vaginal atrophy. Laboratory parameters may be useful in guiding dosage for the treatment of hypogonadism due to hypogonadism, castration and primary ovarian failure.

D. Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay), or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ 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 HDL₂ cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

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 breast, uterus, cervix, vagina, testis, and liver. (See **BOXED WARNINGS, CONTRAINDICATIONS, and WARNINGS.**)

F. Pregnancy

Premarin should not be used during pregnancy. (See **CONTRAINDICATIONS.**)

G. Nursing Mothers

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving the drug. Caution should be exercised when Premarin is administered to a nursing woman.

H. Pediatric Use

Estrogen therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

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

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 to determine whether those over 65 years of age differ from younger subjects in their response to Premarin.

ADVERSE REACTIONS

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

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

1. *Genitourinary system*

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting.

Increase in size of uterine leiomyomata.

Vaginitis, including vaginal candidiasis.

Change in amount of cervical secretion.

Change in cervical ectropion.

Ovarian cancer.

Endometrial hyperplasia.

Endometrial cancer.

2. *Breasts*

Tenderness, enlargement, pain, discharge, galactorrhea.

Fibrocystic breast changes.

Breast cancer.

3. *Cardiovascular*

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

4. *Gastrointestinal*

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

5. *Skin*

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

6. *Eyes*

Retinal vascular thrombosis.
Steepening of corneal curvature.
Intolerance to contact lenses.

7. *Central Nervous System*

Headache.
Migraine.
Dizziness.
Mental depression.
Chorea.
Nervousness.
Mood disturbances.
Irritability.
Exacerbation of epilepsy.

8. *Miscellaneous*

Increase or decrease in weight.

Reduced carbohydrate tolerance.

Aggravation of porphyria.

Edema.

Arthralgias.

Leg cramps.

Changes in libido.

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-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be 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 WARNINGS** 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.

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

Patients should be started at the lowest dose.

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

2. For prevention of postmenopausal osteoporosis.

0.625 mg daily.

Premarin therapy may be given continuously with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug) as is medically appropriate on an individualized basis. When using Premarin solely for the prevention of postmenopausal osteoporosis, alternative non-estrogen treatments should be carefully considered.

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

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

In clinical studies of delayed puberty due to female hypogonadism, breast development was induced by doses as low as 0.15 mg. The dosage may be gradually titrated upward at 6 to 12 month intervals as needed to achieve appropriate bone age advancement and eventual epiphyseal closure. Clinical studies suggest that doses of 0.15 mg, 0.3 mg, and 0.6 mg are associated with mean ratios of bone age advancement to chronological age progression ($\Delta\text{BA}/\Delta\text{CA}$) of 1.1, 1.5, and 2.1, respectively. (Premarin in the dose strength of 0.15 mg is not available commercially). Available data suggest that chronic dosing with 0.625 mg is sufficient to induce artificial cyclic menses with sequential progestin treatment and to maintain bone mineral density after skeletal maturity is achieved.

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

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

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

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

1.25 mg to 2.5 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.

HOW SUPPLIED

Premarin[®] (conjugated estrogens tablets, USP)

—Each oval purple tablet contains 2.5 mg, in bottles of 100 (NDC 0046-0865-81) and 1,000 (NDC 0046-0865-91).

—Each oval yellow tablet contains 1.25 mg, in bottles of 100 (NDC 0046-0866-81); 1,000 (NDC 0046-0866-91); 5,000 (NDC 0046-0866-95); and Unit-Dose Packages of 100 (NDC 0046-0866-99).

—Each oval white tablet contains 0.9 mg, in bottles of 100 (NDC 0046-0864-81).

—Each oval maroon tablet contains 0.625 mg, in bottles of 100 (NDC 0046-0867-81); 1,000 (NDC 0046-0867-91); 5,000 (NDC 0046-0867-95); and Unit-Dose Packages of 100 (NDC 0046-0867-99).

—Each oval green tablet contains 0.3 mg, in bottles of 100 (NDC 0046-0868-81) and 1,000 (NDC 0046-0868-91).

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

Store at room temperature (approximately 25°C).

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

PATIENT INFORMATION
(Updated January 3, 2003)

Premarin[®]
(conjugated estrogens, USP)

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

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

- Estrogens increase the chances of getting cancer of the uterus.

Report any unusual vaginal bleeding right away while you are taking Premarin. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. You and your healthcare provider should talk regularly about whether you still need treatment with estrogens.

What is Premarin?

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

Premarin is used after menopause to:

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

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Premarin.

- **treat moderate to severe dryness, itching, and burning, in or around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with Premarin 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 Premarin only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with Premarin.

Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances for getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

Premarin is also used to:

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

Who should not take Premarin?

Do not start taking Premarin if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.**

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

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

- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breast feeding.** The hormones in Premarin can pass into your milk.
- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, 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 Premarin works. Premarin may also affect how your other medicines work.
- **if you are going to have surgery or will be on bedrest.** You may need to stop taking estrogens.

How should I take Premarin?

- Take one Premarin tablet at the same time each day.
- If you miss a dose, take it as soon as you remember. 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 Premarin.

What are the possible side effects of Premarin?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

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

Common side effects include:

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

Other side effects include:

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

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

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

- Talk with your healthcare provider about whether you should continue taking Premarin.
- See your healthcare provider right away if you get vaginal bleeding while taking Premarin.
- Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about the safe and effective use of Premarin

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


Keep Premarin out of the reach of children.

This leaflet provides a summary of the most important information about Premarin. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Premarin that is written for health professionals. You can get more information by calling the toll free number 800-934-5556.

What are the ingredients in Premarin?

Premarin contains a mixture of conjugated equine estrogens, which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates, 17 α -dihydroequilin, 17 α -estradiol, and 17 β -dihydroequilin. Premarin also contains calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, and titanium dioxide. The tablets come in different strengths and each strength tablet is a different color. The color ingredients are:

- 0.3 mg tablet (green color): D&C Yellow No. 10, FD&C Blue No. 1, FD&C Blue No. 2, and FD&C Yellow No. 6.
- 0.625 mg tablet (maroon color): FD&C Blue No. 2, D&C Red No. 27, and FD&C Red No. 40.
- 0.9 mg tablet (white color): D&C Red No. 6 and D&C Red No. 7.
- 1.25 mg tablet (yellow color): black iron oxide, D&C Yellow No. 10, and FD&C Yellow No. 6.
- 2.5 mg tablet (purple color): FD&C Blue No. 2 and D&C Red No. 7.

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