Premarin®

(conjugated estrogens tablets, USP)

℞ 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.

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. Estrogen replacement therapy acts 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 exist 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 ($0.693/\gamma_2$)

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 ($0.693/\gamma_2$)

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**

	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 3. 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 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

	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 5. 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.

Two subsets of the Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either long-term use of Premarin (0.625 mg conjugated equine estrogens per day) alone or long-term use of Prempro (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of Premarin or Prempro on menopausal symptoms.

The Premarin-only subset is continuing and results have not been reported. The Prempro subset of the study was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified long-term benefits included in the "global index". Results of the Prempro subset, 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 SUBSET OF WHI[a]

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

[a] adapted from JAMA, 2002; 288:321-333
[b] includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
[c] a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
[d] not included in Global Index
* nominal confidence intervals unadjusted for multiple looks and multiple comparisons

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

INDICATIONS AND USAGE
Premarin therapy is indicated in the:

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

2. Treatment of vulvar and vaginal atrophy.

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.

Premarin alone or in combination with a progestin is not indicated and should not be used to prevent coronary heart disease (see WARNINGS).

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

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

The mainstays of prevention of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. The average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

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

CONTRAINDICATIONS

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

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

2. Undiagnosed abnormal genital bleeding.

3. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.

4. Known or suspected estrogen-dependent neoplasia.

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

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

7. Premarin Tablets should not be used in patients with known hypersensitivity to their ingredients.

WARNINGS

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

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

1. **Cardiovascular disorders.**

Postmenopausal 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, estrogen therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

a. Coronary heart disease and stroke. In the Premarin subset of the Women's Health Initiative study (WHI), an increase in the number of myocardial infarctions and stroke has been observed in women receiving estrogen compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

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

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with Prempro (0.625 mg conjugated equine 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 subset of the Women's Health Initiative study (WHI), an increase in VTE has been observed in women receiving estrogen compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the Prempro subset of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving Prempro compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the Prempro group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

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

In the Prempro subset 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 hormone use had a higher relative risk for breast cancer associated with Prempro than those who had never used postmenopausal hormones. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the Premarin subset 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 subset of WHI is continuing.

A reanalysis of original data from 51 epidemiological studies (including Premarin and other postmenopausal hormone therapies) reported an increase in the probability of having breast cancer diagnosed in women currently or recently using postmenopausal hormone (estrogen and/or

estrogen/progestin) therapy. The authors estimate that among 1,000 women who begin hormone therapy at age 50 and continue for 5 years, 10 years or 15 years, the additional number of cases of breast cancer that would occur by age 70 would be 2 cases, 6 cases and 12 cases, respectively. The probability of a diagnosis of breast cancer approached normal by five years after stopping postmenopausal hormone therapy. Additional epidemiological studies suggest that the addition of progestins increases the risk of breast cancer compared to the use of estrogens alone.

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

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

3. **Gallbladder disease.**
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving 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, Premarin should be discontinued.

PRECAUTIONS

A. General

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

There are, however, possible risks that may be associated with the use of progestins in postmenopausal hormone therapy regimens compared to estrogen-alone regimens. These include: an increased risk of breast cancer (see **WARNINGS, Malignant neoplasms**), adverse effects on lipoprotein metabolism (eg, lowering HDL, raising LDL) and impairment of glucose tolerance.

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

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

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

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

6. ***Fluid retention.***
Because estrogens 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. ***Exacerbation of endometriosis.***
Endometriosis may be exacerbated with administration of estrogen therapy.

9. ***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
See text of Patient Information insert after the **HOW SUPPLIED** section.

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

D. Drug/Laboratory Test Interactions
1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.

3. Other binding proteins may be elevated in serum, ie, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

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 **CONTRAINDICATIONS** and **WARNINGS**.)

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

G. Nursing Mothers
The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for the prevention of postpartum breast engorgement.

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

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.

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

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

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

5. *Cardiovascular*
Venous thromboembolism.
Pulmonary embolism.
Superficial thrombophlebitis.
Myocardial infarction.
Stroke.

6. *Eyes*
Steepening of corneal curvature.
Intolerance to contact lenses.

7. *Central Nervous System*
Headache.
Migraine.
Dizziness.
Mental depression.
Chorea.
Nervousness.
Mood disturbances.
Irritability.

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.

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
Use of postmenopausal estrogen therapy, alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically reevaluated. (See **WARNINGS**.)

1. For treatment of moderate-to-severe vasomotor symptoms, and/or vulvar and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen.

   Vasomotor symptoms—0.625 mg daily.

   Vulvar and vaginal atrophy—0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient.

   Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

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

   Female hypogonadism—0.3 mg to 0.625 mg daily, administered cyclically (eg, 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 ($\Delta BA/\Delta CA$) 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.

3. 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.

4. 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.

5. For prevention of 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 treatments should be carefully considered.

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

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

What is the most important information I should know about Premarin?

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS.

If you take any estrogen-containing medicine, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your healthcare provider should check any unusual vaginal bleeding to find out the cause. Women who do not have a uterus have almost no risk of endometrial cancer.

What is Premarin?

Premarin is a mixture of estrogens obtained from natural sources.

What is Premarin used for?

The use of Premarin, alone or in combination with a progestin, may increase your risk of getting breast cancer, blood clots, heart attacks, and strokes. Premarin should be used only as long as needed. Periodically, you and your healthcare provider should discuss whether you still need treatment.

Premarin should not be used to prevent heart disease.

Premarin is used:

- **To reduce moderate to severe menopausal symptoms.**

  Estrogens are hormones produced by a woman's ovaries. Between ages 45 and 55, the ovaries normally stop making estrogens. 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 intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild and in others they can be severe. Taking Premarin can help reduce these symptoms.

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

To treat itching, burning, dryness in or around the vagina due to menopause.

Every 3 to 6 months you and your healthcare provider should discuss whether you still need Premarin to control your vaginal symptoms.

To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.

To treat certain cancers in special situations, in men and women.

To help reduce your chance of getting osteoporosis (thin weak bones).

Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily.

If you use Premarin, alone or in combination with a progestin, only to prevent osteoporosis, discuss with your healthcare provider whether a different treatment might be more appropriate for you.

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

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

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

Who should not take Premarin?

Do not take Premarin

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

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

- **If you have or had certain cancers.**

Estrogens may increase the risks of 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.

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

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

- **If you are allergic to Premarin tablets or any of their ingredients.**

How should I take Premarin?

- Take one Premarin tablet each day at about the same time.

- If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take only your next regularly scheduled dose. Do not take two doses at the same time.

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

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

What are the possible risks and side effects of Premarin?

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

2. **Cancer of the uterus**
   The risk of cancer of the uterus increases when Premarin is used alone, the longer it is used, and when larger doses are taken. Also, Premarin increases the risk of getting a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormonal drug, with Premarin lowers the risk of getting this condition. Therefore, if your uterus has not been removed, your healthcare provider may prescribe a progestin for you to take together with Premarin.

3. **Cancer of the breast**
   Long-term use of Premarin, alone or in combination with progestins, may increase your chance of having breast cancer. Regular breast exams by a healthcare professional and monthly self-exams are recommended for all women. Mammography should be scheduled depending on your age and risk factors.

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

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

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

7. **Blood pressure**
   Some women who are taking Premarin may have increases in blood pressure.

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

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

10. **Endometriosis**
    Taking Premarin may worsen endometriosis. Talk with your healthcare provider if you have had endometriosis.

11. **Effects on blood sugar**
    Taking Premarin may affect blood sugar levels, which might make a diabetic condition worse.

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

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Nausea and vomiting, cramps, or bloating in the abdomen.

- Hair loss or abnormal hairiness.

- Breast tenderness or enlargement, pain and discharge.
- Enlargement of benign tumors ("fibroids") of the uterus.
- Change in amount of cervical secretion.
- Vaginal yeast infections.
- Retention of fluid (edema).
- A spotty darkening of the skin, particularly on the face, reddening of the skin, skin rashes.
- Headache, migraines, dizziness, or changes in vision (including intolerance to contact lenses).
- Involuntary muscle spasms.
- Increase or decrease in weight.
- Changes in sex drive.

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

If you take Premarin, you can reduce your risks by doing these things:

- **See your healthcare provider regularly.**

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

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

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

- **Be alert to signs of trouble.**

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

- Abnormal bleeding from the vagina (possible uterine cancer).
- Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clots in the legs, heart, or lungs).
- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech,

weakness or numbness of an arm or leg (possible clot in the brain or eye).

- Breast lumps (possible breast cancer). Check your breasts every month. Ask your healthcare provider to show you how to examine your breasts.
- Yellowing of the skin or whites of the eyes (possible liver problem).
- Pain, swelling, or tenderness in the abdomen (stomach area, possible gallbladder problem).

Other information

1. Your healthcare provider prescribed this drug for you and you alone. Do not give this drug to anyone else.
2. Keep this and all drugs out of reach of children. In case of overdose, call your doctor, or healthcare provider, hospital or poison control center right away.

HOW SUPPLIED

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