

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-417

APPROVED LABELING

DRAFT

12-17-2001

Premarin®
(conjugated estrogens tablets, USP)

R_x only

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1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

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 "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

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2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

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Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

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DESCRIPTION

Premarin (conjugated estrogens tablets, USP) for oral administration contains a mixture of 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, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg strengths of conjugated estrogens.

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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.

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—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.

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—0.45 mg tablets also contain: FD&C Blue No. 2.

—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.

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—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.

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—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

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Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

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Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

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Estrogens occur naturally in several forms. 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. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone — especially in its sulfate ester form — is the most abundant

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circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

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Information Regarding Lipid Effects

The results of a clinical trial conducted in a primarily Caucasian population at low risk for cardiovascular disease show that Premarin doses of 0.625 mg, 0.45 mg, and 0.3 mg significantly increase HDL-C and the HDL₂-C subfraction and significantly decreases LDL-C.

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Table 1 summarizes mean percent changes from baseline lipid parameter values after 1 and 2 years of treatment with Premarin doses of 0.625 mg, 0.45 mg, and 0.3 mg.

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TABLE 1. MEAN PERCENT CHANGE FROM BASELINE LIPID PROFILE VALUES AFTER ONE AND TWO YEARS OF TREATMENT WITH PREMARIN

Lipid Parameter	-----0.625 mg-----		-----0.45 mg-----		-----0.3 mg-----		-----Placebo-----	
	1 Year (n = 66)	2 Years (n = 41)	1 Year (n = 73)	2 Years (n = 59)	1 Year (n = 75)	2 Years (n = 60)	1 Year (n = 78)	2 Years (n = 60)
Total cholesterol	-1.2 ^a	1.00 ^a	-0.4 ^a	1.8	1.7	2.2	3.1 ^b	5.7 ^b
HDL-cholesterol	15.3 ^{a,b}	18.8 ^{a,b}	15.4 ^{a,b}	20.0 ^{a,b}	10.0 ^{a,b}	14.1 ^{a,b}	2.0	3.8 ^b
HDL ₂ -cholesterol	51.6 ^{a,b}	60.6 ^{a,b}	45.4 ^{a,b}	57.8 ^{a,b}	30.8 ^{a,b}	41.4 ^{a,b}	3.9	4.8
LDL-cholesterol	-8.9 ^{a,b}	-7.5 ^{a,b}	-8.5 ^{a,b}	-7.3 ^{a,b}	-4.1 ^{a,b}	-4.0 ^a	2.9 ^b	7.1 ^b
LDL-C/HDL-C	-19.9 ^{a,b}	-20.7 ^{a,b}	-20.1 ^{a,b}	-21.4 ^{a,b}	-12.2 ^{a,b}	-15.4 ^{a,b}	1.6	3.3
Triglycerides	34.3 ^{a,b}	47.6 ^{a,b}	30.2 ^{a,b}	32.5 ^{a,b}	25.1 ^b	19.0 ^b	10.7	5.5

a: Significantly (p < 0.05) different from placebo.
 b: Significantly (p < 0.05) different from baseline value.

All treated groups showed favorable increases in HDL-C and HDL₂-C and decreases in LDL-C and LDL-C/HDL-C ratio, in contrast to no change or opposite results in the placebo group.

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PHARMACOKINETICS**Absorption**

125 Conjugated estrogens used in therapy are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. Maximum plasma concentrations of the various conjugated and unconjugated estrogens are attained within 4 to 10 hours after oral administration.

130 Estrogens used in therapy are also well absorbed through the skin and mucous membranes. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Distribution

135 Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin (SHBG) and albumin, only unbound estrogens enter target tissue cells. (Conjugated estrogens bind mainly to albumin; unconjugated estrogens bind to both albumin and SHBG.) The apparent terminal-phase disposition half-life ($t_{1/2}$) of the various estrogens is prolonged by the slow absorption from Premarin and ranges from 10 to 24 hours.

Metabolism

145 Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first-pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between esterified and non-esterified forms. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogen is excreted into the bile, then reabsorbed from the intestine and returned to the liver through the portal venous system. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

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165 When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first-pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral

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routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

170 **Excretion**

Water-soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favor excretion through the kidneys since tubular reabsorption is minimal.

175 **TABLE 2. 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	8.8	28.0	5016
180 baseline-adjusted estrone	120	8.8	17.4	2956
equilin	66	7.9	13.6	1210

185 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	7.3	15.0	134
baseline-adjusted total estrone	7.1	7.3	13.6	122
total equilin	5.0	6.2	10.1	65

C_{max} = peak plasma concentration

t_{max} = time peak concentration occurs

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

AUC = total area under the curve

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CLINICAL STUDIES
Information Regarding Osteoporosis

195 The Women's Health and Osteoporosis, Progestin and Estrogen (Women's HOPE) study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy postmenopausal women with an intact uterus. They were treated with Premarin 0.625 mg, with or without MPA 2.5 mg, Premarin 0.45 mg alone or with MPA 2.5 mg or 1.5 mg, Premarin 0.3 mg, with or without MPA 1.5 mg, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L2 to L4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

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205 **Intent-to-treat subjects**

All active treatment groups showed significant differences from placebo in each of the 4 BMD endpoints. Active treatment groups showed statistically significant mean increases in BMD while the placebo group showed mean decreases (except for femoral trochanter, which was unchanged).

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Efficacy evaluable subjects

215 All analyses of the BMD data showed that conjugated estrogens were significantly more
effective than placebo in the prevention of bone loss. This was true for all 4 BMD
measures and for both types of analyses (slope and by cycle). The primary analysis
(slope) of the primary efficacy measure (L2 to L4 BMD) in the primary population
(efficacy evaluable) showed significant differences between Premarin treatment groups
and placebo, with active treatments producing mean increases in the annualized percent
change from baseline and the placebo treatment showing mean decreases. With active
220 treatment, the mean percent increases were 1.68% with 0.625 mg, 1.28% with 0.45 mg,
and 0.76% with 0.3 mg. The placebo group showed a mean percent decrease in the
annualized percent change from baseline of -1.49%. These results show that the lower
dose regimens of Premarin were effective in increasing BMD compared with placebo
and, therefore, support the efficacy of lower doses of Premarin.

225 The slope analysis for the other 3 BMD endpoints yielded mean annualized percent
changes from baseline in femoral trochanter that were larger than those seen for L2 to L4
and changes in femoral neck and total body that were smaller than those seen for L2 to
L4. Significant differences between groups indicated that each of the active treatment
groups were more effective than placebo for all 3 of these additional BMD endpoints.
230 With regard to L2 to L4, femoral neck, and total body, active treatment produced mean
percent increases in BMD while treatment with placebo produced mean percent
decreases. For femoral trochanter, the placebo group showed no change but each of the
active treatment groups showed a mean percent increase. The annualized percent change
in BMD from slope analysis is shown in Table 3. Bone data by cycle for L2 to L4 are
235 presented in the figure following Table 3.

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TABLE 3. ANNUALIZED PERCENT CHANGE IN BONE MINERAL DENSITY FROM SLOPE ANALYSIS: COMPARISON BETWEEN ACTIVE-TREATMENT AND PLACEBO GROUPS IN THE EFFICACY-EVALUABLE POPULATION

Region Evaluated Treatment Group ^a	No. of Pairs	Baseline (g/cm ²)		Change from Baseline (%)		p-Values vs Placebo
		Mean	SD	Adjusted Mean ^b	SE	
L2 to L4 BMD						
0.625	66	1.16	0.15	1.68	0.24	<0.001
0.45	77	1.13	0.16	1.28	0.22	<0.001
0.3	76	1.14	0.15	0.76	0.22	<0.001
Placebo	78	1.15	0.14	-1.49	0.22	
Femoral neck BMD						
0.625	66	0.90	0.14	1.11	0.30	<0.001
0.45	77	0.89	0.13	1.16	0.27	<0.001
0.3	76	0.86	0.12	0.28	0.28	<0.001
Placebo	78	0.88	0.14	-1.30	0.27	
Femoral trochanter BMD						
0.625	66	0.77	0.13	2.30	0.36	<0.001
0.45	77	0.76	0.12	2.04	0.33	<0.001
0.3	76	0.74	0.11	1.67	0.33	0.003
Placebo	78	0.75	0.13	0.31	0.33	
Total body BMD						
0.625	66	1.14	0.08	0.42	0.11	<0.001
0.45	77	1.14	0.08	0.47	0.10	<0.001
0.3	76	1.14	0.08	0.24	0.10	<0.001
Placebo	78	1.13	0.08	-0.85	0.10	

a: Identified by dose (mg) of CE or CE/MPA.

b: Adjusted annualized mean change from baseline obtained from analysis of covariance with treatment and study site as factors and weight and years since menopause as covariants.

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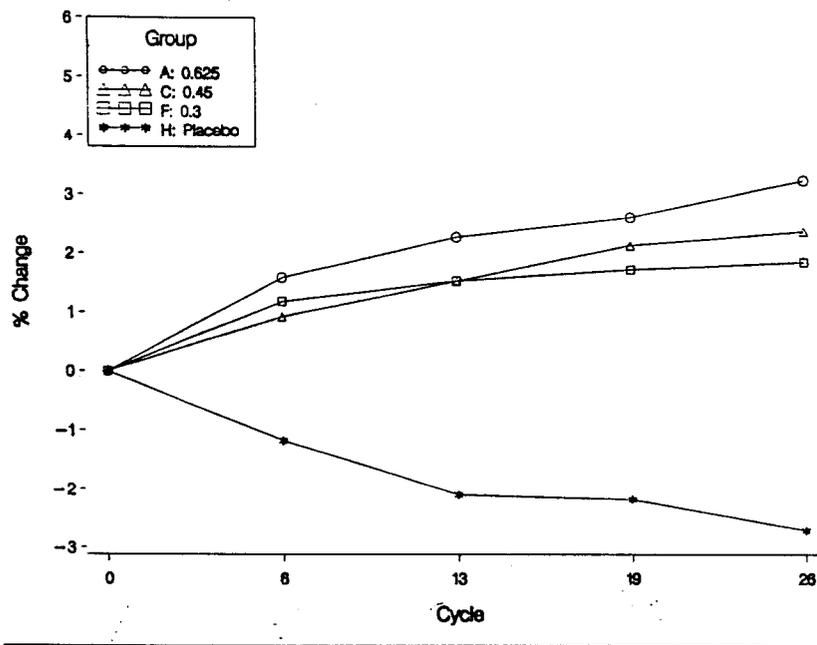
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MEAN PERCENT CHANGE FROM BASELINE IN L2-L4 LUMBAR SPINE BMD:
EFFICACY EVALUABLE POPULATION



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INDICATIONS AND USAGE

Estrogen drug products are indicated in the

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

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There is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.

2. Treatment of vulvar and vaginal atrophy.

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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.

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5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).

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6. Prevention of osteoporosis. Since estrogen administration is associated with risk, selection of patients ideally should be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification

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270 by other risk factors, and tend to show a universally salutary effect on bone. Thus, patient selection must be individualized based on the balance of risks and benefits. A more favorable risk/benefit ratio exists in a hysterectomized woman because she has no risk of endometrial cancer (see Boxed Warning).

275 Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown an approximately 60 percent reduction in hip and wrist fractures in women whose estrogen replacement 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 prevents further loss of bone mass for as long as the treatment is continued. When 280 estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. There is no evidence that estrogen replacement therapy restores bone mass to premenopausal levels.

285 At skeletal maturity there are sex and race differences in both the total amount of bone present and its density, in favor of men and blacks. Thus, women are at higher risk than men because they start with less bone mass and, for several years following natural or induced menopause, the rate of bone mass decline is accelerated. White and Asian women are at higher risk than black women.

290 Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton which 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 295 nutrition (below average body weight, dietary calcium intake).

The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of 300 elemental calcium to remain in neutral calcium balance. By comparison, premenopausal women require about 1,000 mg/day and the average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful.

305 Weight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established, however in two studies an hour of walking and 310 running exercises twice or three times weekly significantly increased lumbar spine bone mass.

CONTRAINDICATIONS

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

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- 1. Known or suspected pregnancy (see Boxed Warning).
Estrogens may cause fetal harm when administered to a pregnant woman.
- 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 or past history of thrombophlebitis or thromboembolic disorders.
- 6. Premarin Tablets should not be used in patients hypersensitive to their ingredients.

WARNINGS

1. *Induction of malignant neoplasms.*

Breast cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, there are conflicting data whether there is an increased risk in women using estrogens for prolonged periods of time, especially in excess of 10 years.

The Women's HOPE study was a multicenter clinical trial of the safety and efficacy of lower-dose regimens of conjugated estrogens/medroxyprogesterone acetate and comparable conjugated estrogen doses in postmenopausal women. It included a 1-year basic study that focused on menopausal symptoms, endometrial histology and bleeding profiles, and a 2-year osteoporosis and metabolic substudy. There were no statistically significant differences in the incidence of breast cancer among the active treatment groups or as compared with the placebo group, in either the first or second year of the Women's HOPE study. The statistical power of the study was low for this endpoint. The number of cases of breast cancer in the conjugated estrogen and placebo groups are listed by treatment and year of occurrence in Table 4.

TABLE 4. NUMBER OF CASES OF BREAST CANCER IN THE WOMEN'S HOPE STUDY: YEARS 1 AND 2

Treatment	Year 1		Year 2		Post-Study
	Cases	No. of Patients	Cases	No. of Patients ^a	
0.625 mg CE	1	348	0	65	0
0.45 mg CE	0	338	1	74	0
0.3 mg CE	0	326	0	73	1 ^b
Placebo	1	332	1	75	0

a: The population of year 2 consisted of those women in the substudy in year 1 who continued into year 2.
b: Diagnosed approximately 9 months after completing the 2-year study.

In the three year clinical Postmenopausal Estrogen Progestin Intervention (PEPI) trial of 875 women to assess differences among placebo, unopposed Premarin, and three

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355 different combination hormone therapy regimens, one (1) new case of breast cancer was detected in the placebo group (n=174), one in the Premarin alone group (n=175), none in the continuous Premarin plus continuous medroxyprogesterone acetate group (n=174), and two (2) in the continuous Premarin plus cyclic medroxyprogesterone acetate group (n=174).

360 Women on this therapy should have regular breast examinations and should be instructed in breast self-examination, and women over the age of 40 should have regular mammograms.

365 *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. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal.

370 In the first year of the Women's HOPE study, 1344 women between 40 and 65 years of age (88% were Caucasian) were treated with either Premarin 0.625 mg (n = 348), 0.45 mg (n = 338), or 0.3 mg (n = 326) or placebo (n = 332). After 1 year of treatment, the rate of consensus endometrial hyperplasia (see footnote "a" for Table 5) was 8% for patients who received Premarin 0.625 mg, 3% for those who received 0.45 mg, and less than 1% for patients who received 0.3 mg (Table 5). There was no case of endometrial hyperplasia in the placebo group.

380 At the end of the second year of the study, in a substudy population, endometrial biopsies were evaluable for consensus for 55 women who received Premarin 0.625 mg, 67 who received 0.45 mg, 63 women who received 0.3 mg, and 61 women who received placebo. The rate of hyperplasia for these substudy patients was 27% in women who received 0.625 mg, compared with 15% in the 0.45-mg dose group and 3% in the 0.3-mg dose group (Table 6). There were no cases of hyperplasia in women treated with placebo.

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TABLE 5. INCIDENCE OF ENDOMETRIAL HYPERPLASIA AFTER ONE YEAR OF TREATMENT^a

Patient	Groups					
	PREMPRO 0.625 mg/2.5 mg	Premarin 0.625 mg	PREMPRO 0.45 mg/1.5 mg	Premarin 0.45 mg	PREMPRO 0.3 mg/1.5 mg	Premarin 0.3 mg
Total number of patients	331	348	331	338	327	326
Number of patients with biopsies evaluable for consensus	278	249^b	272	279^b	271^b	269^b
No. (%) of patients with biopsies						
• all hyperplasias (consensus)	0 (0) ^c	20 (8)	1 (<1) ^d	9 (3)	1 (<)	1 (<1)
• all hyperplasias (pathologist 1)	0 (0) ^c	33 (13)	1 (<1) ^c	18 (6)	0 (0)	3 (1.2)
• all hyperplasias (pathologist 2)	0 (0) ^c	28 (11)	1 (<1) ^c	18 (6)	1 (<1)	6 (2.2)

a: Two pathologists evaluated each endometrial biopsy. Where there was lack of agreement between the two, a third pathologist adjudicated (consensus).

b: Number evaluated = 272 for pathologist 1 (PREMPRO 0.3 mg/1.5 mg), 270 for pathologist 1 (0.3 mg Premarin), 280 for pathologist 1 (0.45 mg Premarin); 253 for pathologist 1 (0.625 mg Premarin).

c: Significant (p < 0.001) in comparison with corresponding dose of Premarin alone.

d: Significant (p < 0.02) in comparison with corresponding dose of Premarin alone.

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TABLE 6. INCIDENCE OF ENDOMETRIAL HYPERPLASIA AFTER TWO YEARS OF TREATMENT^a

Patient	Groups					
	PREMPRO 0.625 mg/2.5 mg	Premarin 0.625 mg	PREMPRO 0.45 mg/1.5 mg	Premarin 0.45 mg	PREMPRO 0.3 mg/1.5 mg	Premarin 0.3 mg
<u>Total number of patients</u>	75	65	75	74	79	73
<u>Number of patients with biopsies evaluable for consensus</u>	62	55 ^b	69	67 ^b	75	63 ^b
<u>No. (%) of patients with biopsies</u>						
• <u>all hyperplasias (consensus)</u>	0 (0) ^c	15 (27)	(0) ^c	10 (15)	(0)	2 (3)
• <u>all hyperplasias (pathologist 1)</u>	0 (0) ^c	16 (30)	(0) ^c	14 (20)	(0) ^d	5 (8)
• <u>all hyperplasias (pathologist 2)</u>	0 (0) ^c	17 (31)	(0) ^c	10 (15)	(0) ^d	4 (6)

a: Two pathologists evaluated each endometrial biopsy. Where there was lack of agreement between the two, a third pathologist adjudicated (consensus).

b: Number evaluated = 54 for pathologists 1 and 2 for 0.625 mg Premarin; 69 for pathologist 2 and 66 for pathologist 1 for 0.45 mg Premarin; 64 for pathologists 1 and 2 for 0.3 mg Premarin.

c: Significant (p < 0.001) in comparison with corresponding dose of Premarin alone.

d: Significant (p < 0.05) in comparison with corresponding dose of Premarin alone.

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Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

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Congenital lesions with malignant potential. Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

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2. *Gallbladder disease.* Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens. In another large one-year clinical trial that evaluated doses of conjugated estrogens of 0.625 mg, 0.45 mg, and 0.3 mg, and placebo, gallbladder disease was reported by 1 of 338 patients who took conjugated estrogens 0.45 mg and 1 of 326 patients who took conjugated estrogens 0.3 mg.

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3. *Thromboembolic disorders.*

Venous thromboembolism. Several epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestins and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women per year.

415

420

Cardiovascular disease. Embolic cerebrovascular events have been reported in women receiving postmenopausal estrogens.

425

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. In a large one-year clinical trial evaluating 1,012 women who received conjugated estrogens 0.625 mg, 0.45 mg, and 0.3 mg, pulmonary embolism was diagnosed for one patient receiving 0.45 mg and stroke was diagnosed for one patient receiving conjugated estrogens 0.625 mg; myocardial infarction was diagnosed in one placebo patient. Among 212 patients who entered the second year of the 2-year substudy and received conjugated estrogens alone, there were no thromboembolic events during study year 2.

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The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) during estrogen replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, estrogen replacement therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

4. *Elevated blood pressure.* Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. In a recent large clinical trial evaluating lower doses of conjugated estrogens, transient increases of 40 mm Hg or more in systolic blood pressure were reported in 15 of 1,012 patients (1.5%) receiving conjugated estrogens (4 receiving 0.625 mg, 3 receiving 0.45 mg, and 8 receiving 0.3 mg), and in 4 of 332 patients (1.2%) receiving placebo. In this same study, transient increases of 20 mm Hg or more from baseline in diastolic blood pressure were reported for 50 of 1012 patients (5.0%) receiving conjugated estrogens (12 receiving 0.625 mg, 17 receiving 0.45 mg, and 21 receiving 0.3 mg), and for 11 of 332 patients (3.3%) receiving placebo. Blood pressure should be monitored at regular intervals with estrogen use.

5. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

A. General

1. *Addition of a progestin.* Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphological and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. The potential risks include adverse effects on lipoprotein metabolism, impairment of glucose tolerance, and possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point (see PRECAUTIONS below).

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

2. *Cardiovascular risk.* The effects of estrogen replacement on the risk of cardiovascular disease have not been adequately studied. However, data from the Heart and Estrogen/Progestin Replacement Study (HERS), a controlled clinical trial of secondary Wyeth addition ~~Wyeth deletion~~

485 prevention of 2,763 postmenopausal women with documented heart disease,
demonstrated no benefit. During an average follow-up of 4.1 years, treatment with oral
conjugated estrogens plus medroxyprogesterone acetate did not reduce the overall rate of
coronary heart disease (CHD) events in postmenopausal women with established
490 coronary disease. There were more CHD events in the hormone treated group than in the
placebo group in year 1, but fewer events in years 3 through 5.

A causal relationship between estrogen replacement therapy and reduction of
cardiovascular disease in postmenopausal women has not been proven. Furthermore, the
effect of added progestins on this putative benefit is not yet known.

495 In recent years many published studies have suggested that there may be a cause-effect
relationship between postmenopausal oral estrogen replacement therapy *without added
progestins* and a decrease in cardiovascular disease in women. Although most of the
observational studies which assessed this statistical association have reported a 20% to
500 50% reduction in coronary heart disease risk and associated mortality in estrogen takers,
the following should be considered when interpreting these reports:

(1) Because only one of these studies was randomized and it was too small to yield
statistically significant results, all relevant studies were subject to selection bias. Thus,
505 the apparently reduced risk of coronary artery disease cannot be attributed with certainty
to estrogen replacement therapy. It may instead have been caused by life-style and
medical characteristics of the women studied with the result that healthier women were
selected for estrogen therapy. In general, treated women were of higher socioeconomic
and educational status, more slender, more physically active, more likely to have
510 undergone surgical menopause, and less likely to have diabetes than the untreated
women. Although some studies attempted to control for these selection factors, it is
common for properly designed randomized trials to fail to confirm benefits suggested by
less rigorous study designs. Thus, ongoing and future large-scale randomized trials may
fail to confirm this apparent benefit.

515 (2) Current medical practice often includes the use of concomitant progestin therapy in
women with intact uteri (see **PRECAUTIONS** and **WARNINGS**). While the effects of
added progestins on the risk of ischemic heart disease are not known, all available
progestins reverse at least some of the favorable effects of estrogens on HDL and LDL
520 cholesterol levels.

(3) While the effects of added progestins on the risk of breast cancer are also unknown,
available epidemiological evidence suggests that progestins do not reduce, and may
enhance, the moderately increased breast cancer incidence that has been reported with
525 prolonged estrogen replacement therapy (see **WARNINGS**).

*Because relatively long-term use of estrogens by a woman with a uterus has been shown
to increase the risk of endometrial cancer, physicians often recommend that these women
should take progestins as well as estrogens. When considering prescribing concomitant
estrogens and progestins for hormone replacement therapy, physicians and patients are
530 advised to carefully weigh the potential benefits and risks of the added progestin. Large-*

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scale randomized, placebo-controlled, clinical trials and future epidemiological studies are required to clarify these issues.

- 535 3. *Physical examination.* A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.
- 540 4. *Hypercoagulability.* Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have
- 545 increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.
- 550 5. *Thromboembolism.* Based on data obtained with oral contraceptives, estrogens should be discontinued at least four weeks before surgery of the type associated with an increased risk of thromboembolism if feasible, or during periods of prolonged immobilization (see **WARNINGS**).
- 555 6. *Familial hyperlipoproteinemia.* Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.
- 560 7. *Fluid retention.* Because estrogens may cause some degree of fluid retention, conditions which might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.
- 565 8. *Exacerbation of endometriosis.* Endometriosis may be exacerbated with administration of estrogen therapy.
- 570 9. *Uterine bleeding and mastodynia.* Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.
- 575 10. *Impaired liver function.* Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.
11. *Uterine fibroids.* Pre-existing uterine leiomyomata may increase in size during estrogen use.
12. *Hypocalcemia.* Estrogens should be used with caution in individuals with metabolic bone disease associated with severe hypocalcemia.

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580 **B. Information for the Patient.** See text of Patient Package Insert which appears after the **HOW SUPPLIED** section.

585 **C. Laboratory Tests.** Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable. For prevention of osteoporosis, however, see **DOSAGE AND ADMINISTRATION** section.

D. Drug/Laboratory Test Interactions.

590 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.

595 2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, 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.

600 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).

605 4. Increased plasma HDL and HDL₂ subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

610 5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

615 **E. Carcinogenesis, Mutagenesis, and 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**.

620 **F. Pregnancy Category X.** Estrogens should not be used during pregnancy. See **CONTRAINDICATIONS** and **Boxed Warning**.

G. Nursing Mothers. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in

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625 human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

H. Pediatric Use. See DOSAGE AND ADMINISTRATION.

630 **ADVERSE REACTIONS**

In a large one-year clinical trial that included 1,012 women treated with conjugated estrogens and 332 treated with placebo, adverse events that occurred at a rate of $\geq 5\%$ are summarized in Table 7.

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**TABLE 7. NUMBER (%) OF PATIENTS REPORTING ≥ 5% TREATMENT
EMERGENT ADVERSE EVENTS**

<u>Body System</u>	<u>-----Premarin Treatment Group-----</u>			
	<u>0.625 mg</u> <u>(n = 348)</u>	<u>0.45 mg</u> <u>(n = 338)</u>	<u>0.3 mg</u> <u>(n = 326)</u>	<u>Placebo</u> <u>(n = 332)</u>
<u>Any adverse event</u>	<u>323 (93)</u>	<u>305 (90)</u>	<u>292 (90)</u>	<u>281 (85)</u>
<u>Body as a Whole</u>				
<u>Abdominal pain</u>	<u>56 (16)</u>	<u>50 (15)</u>	<u>54 (17)</u>	<u>37 (11)</u>
<u>Accidental injury</u>	<u>21 (6)</u>	<u>41 (12)</u>	<u>20 (6)</u>	<u>29 (9)</u>
<u>Asthenia</u>	<u>25 (7)</u>	<u>23 (7)</u>	<u>25 (8)</u>	<u>16 (5)</u>
<u>Back pain</u>	<u>49 (14)</u>	<u>43 (13)</u>	<u>43 (13)</u>	<u>39 (12)</u>
<u>Flu syndrome</u>	<u>38 (11)</u>	<u>38 (11)</u>	<u>34 (10)</u>	<u>35 (11)</u>
<u>Headache</u>	<u>91 (26)</u>	<u>109 (32)</u>	<u>96 (29)</u>	<u>93 (28)</u>
<u>Infection</u>	<u>61 (18)</u>	<u>75 (22)</u>	<u>74 (23)</u>	<u>74 (22)</u>
<u>Pain</u>	<u>58 (17)</u>	<u>61 (18)</u>	<u>66 (20)</u>	<u>61 (18)</u>
<u>Digestive System</u>				
<u>Diarrhea</u>	<u>21 (6)</u>	<u>25 (7)</u>	<u>19 (6)</u>	<u>21 (6)</u>
<u>Dyspepsia</u>	<u>33 (9)</u>	<u>32 (9)</u>	<u>36 (11)</u>	<u>46 (14)</u>
<u>Flatulence</u>	<u>24 (7)</u>	<u>23 (7)</u>	<u>18 (6)</u>	<u>9 (3)</u>
<u>Nausea</u>	<u>32 (9)</u>	<u>21 (6)</u>	<u>21 (6)</u>	<u>31 (9)</u>
<u>Musculoskeletal System</u>				
<u>Arthralgia</u>	<u>47 (14)</u>	<u>42 (12)</u>	<u>22 (7)</u>	<u>39 (12)</u>
<u>Leg cramps</u>	<u>19 (5)</u>	<u>23 (7)</u>	<u>11 (3)</u>	<u>7 (2)</u>
<u>Myalgia</u>	<u>18 (5)</u>	<u>18 (5)</u>	<u>29 (9)</u>	<u>25 (8)</u>
<u>Nervous System</u>				
<u>Anxiety</u>	<u>18 (5)</u>	<u>12 (4)</u>	<u>12 (4)</u>	<u>12 (4)</u>
<u>Depression</u>	<u>25 (7)</u>	<u>27 (8)</u>	<u>17 (5)</u>	<u>22 (7)</u>
<u>Dizziness</u>	<u>19 (5)</u>	<u>20 (6)</u>	<u>12 (4)</u>	<u>17 (5)</u>
<u>Insomnia</u>	<u>21 (6)</u>	<u>25 (7)</u>	<u>24 (7)</u>	<u>33 (10)</u>
<u>Nervousness</u>	<u>12 (3)</u>	<u>17 (5)</u>	<u>6 (2)</u>	<u>7 (2)</u>
<u>Respiratory System</u>				
<u>Cough increased</u>	<u>13 (4)</u>	<u>22 (7)</u>	<u>14 (4)</u>	<u>14 (4)</u>
<u>Pharyngitis</u>	<u>35 (10)</u>	<u>35 (10)</u>	<u>40 (12)</u>	<u>38 (11)</u>
<u>Rhinitis</u>	<u>21 (6)</u>	<u>30 (9)</u>	<u>31 (10)</u>	<u>42 (13)</u>
<u>Sinusitis</u>	<u>22 (6)</u>	<u>36 (11)</u>	<u>24 (7)</u>	<u>24 (7)</u>
<u>Upper respiratory infection</u>	<u>42 (12)</u>	<u>34 (10)</u>	<u>28 (9)</u>	<u>35 (11)</u>
<u>Skin and appendages</u>				
<u>Pruritus</u>	<u>14 (4)</u>	<u>17 (5)</u>	<u>16 (5)</u>	<u>7 (2)</u>
<u>Urogenital System</u>				
<u>Breast pain</u>	<u>38 (11)</u>	<u>41 (12)</u>	<u>24 (7)</u>	<u>29 (9)</u>
<u>Leukorrhea</u>	<u>18 (5)</u>	<u>22 (7)</u>	<u>13 (4)</u>	<u>9 (3)</u>
<u>Vaginal hemorrhage</u>	<u>47 (14)</u>	<u>14 (4)</u>	<u>7 (2)</u>	<u>0</u>
<u>Vaginal moniliasis</u>	<u>20 (6)</u>	<u>18 (5)</u>	<u>17 (5)</u>	<u>6 (2)</u>
<u>Vaginitis</u>	<u>24 (7)</u>	<u>20 (6)</u>	<u>16 (5)</u>	<u>4 (1)</u>

635

The following additional adverse reactions have been reported with estrogen therapy (see **WARNINGS** regarding induction of malignant neoplasms, gallbladder disease, thromboembolic disorders, elevated blood pressure, and hypercalcemia; see **WARNINGS** and **PRECAUTIONS** regarding cardiovascular risk).

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- 1. *Genitourinary system.*
 - Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow;
 - breakthrough bleeding, spotting.
 - 645 Increase in size of uterine leiomyomata.
 - Vaginal candidiasis.
 - Change in amount of cervical secretion.

- 2. *Breasts.*
 - 650 Tenderness, enlargement.

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

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

- 5. *Cardiovascular.*
 - Venous thromboembolism.
 - Pulmonary embolism.
 - 670

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

- 675 7. *Central Nervous System.*
 - Headache.
 - Migraine.
 - Dizziness.
 - Mental depression.
 - 680 Chorea.

- 8. *Miscellaneous.*
 - Increase or decrease in weight.
 - Reduced carbohydrate tolerance.
 - 685 Aggravation of porphyria.
 - Edema.
 - Changes in libido.

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Anaphylactoid/anaphylactic reactions.

690 **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.

695 **DOSAGE AND ADMINISTRATION**

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 and medication should be discontinued as promptly as possible.

700

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.

705

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.

710

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

2. For treatment of female hypoenestrogenism due to hypogonadism, castration, or primary ovarian failure:

715

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.

720

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.

725

730

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:

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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:

740

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.

745

5. For prevention of osteoporosis: 0.3 mg to 0.625 mg daily, depending upon the response of the patient. 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.

HOW SUPPLIED

750 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).

755

—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).

760

—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).

765

—Each oval blue tablet contains 0.45 mg, in bottles of 100 (NDC 0046-0936-81).

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

770

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.

775

INFORMATION FOR THE PATIENT

INTRODUCTION

780

This leaflet describes when and how to use estrogens, and the risks and benefits of estrogen treatment.

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785 Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you decide to start taking estrogens, check with your doctor to make sure you are using the lowest possible effective dose, and that you use them for only as long as necessary. How long you need to use estrogens will depend on the reason for use.

790 **1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE (“CHANGE OF LIFE”).**
 If you use any estrogen-containing drug, 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 doctor should evaluate any unusual vaginal bleeding to find out the cause.

795 **2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.**
 Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby’s urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

800 **USES OF ESTROGEN**
 (Not every estrogen drug is approved for every use listed in this section. If you want to know which of these possible uses are approved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling. You can also look up the specific estrogen product in a book called *The Physician’s Desk Reference*, which is available in many book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.)

815 *To reduce moderate to severe menopausal symptoms.*
 Estrogens are hormones made by the ovaries of normal women. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the “change of life” or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes “surgical menopause.”

820 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”). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. In some women the symptoms are mild; in others they can be severe. These symptoms may last only a few months or longer. Taking Premarin can alleviate these symptoms. If you are not taking estrogen for other reasons, such as the prevention of osteoporosis, you should take Premarin only as long as you need it for relief from your menopausal symptoms.

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830 *To treat vulvar and vaginal atrophy (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.*

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

835

To treat certain types of abnormal uterine bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.

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

840

To prevent thinning of bones.

Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you. Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have relatively early menopause, often because their ovaries were removed during an operation ("surgical menopause"), are more likely to develop osteoporosis than women whose menopause happens at the average age.

860

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

During pregnancy (see Boxed Warning).

865

If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.

870

If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Boxed Warning).

Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.

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If you have had cancer.

880 Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you have ever had cancer of the breast or uterus, unless your doctor recommends that the drug may help in the cancer treatment. (For certain patients with breast or prostate cancer, estrogens may help.)

If you have any circulation problems.

885 Estrogen drugs should not be used except in unusually special situations in which your doctor judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see **RISKS OF ESTROGENS**, below).

When they do not work.

890 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 these claims and such long-term estrogen use may have serious risks.

After childbirth or when breastfeeding a baby.

895 Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see **RISKS OF ESTROGENS**, below).

900 If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health-care provider.

RISKS OF ESTROGENS*Cancer of the uterus.*

905 Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. One study showed that after women stop taking estrogens, this higher cancer risk quickly returns to the usual level of risk (as if you had never used estrogen therapy). Three other studies showed that the cancer risk stayed high for 8 to
910 more than 15 years after stopping estrogen treatment. Because of this risk,

IT IS IMPORTANT TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU NEED IT.

915 Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see **OTHER INFORMATION**, below). If you have had your uterus removed (total hysterectomy), there is no risk of developing cancer of the uterus.

Cancer of the breast.

920 Most studies have not shown a higher risk of breast cancer in women who have used estrogens at some time in their lifetimes. However, some studies suggest there may be a

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higher risk of breast cancer in women who use estrogens for a long period of time, especially 10 years or more.

925 All women should do monthly self-exams of their breasts and have regular breast exams by a health professional. Women ages 40 and above should have periodic mammograms to check for early signs of breast cancer. Ask your health professional how to do a breast self-exam.

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

Inflammation of the pancreas (Pancreatitis).
935 Women with high triglyceride levels may have an increased risk of developing inflammation of the pancreas.

Abnormal blood clotting.
940 Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (cutting off blood to the brain), a heart attack (cutting off blood to the heart), a pulmonary embolus (cutting off blood to the lungs), retinal thrombosis (cutting off blood vessels in the eye),
945 or other problems. Any of these conditions may cause death or serious long term disability.

Endometriosis.
950 Administration of estrogens may worsen endometriosis. If you have had endometriosis, speak with your health professional.

Cardiovascular disease.
955 A recent 4-year study suggests that women with a history of coronary heart disease may have an increased risk of serious cardiac events during the first year of treatment with estrogen/progestin therapy. Therefore, if you have had a heart attack, or you have been told you have blocked coronary arteries (arteries to your heart) or have any heart problem, you should consult your physician regarding the potential benefits and risks of estrogen/progestin therapy.

960 **SIDE EFFECTS**

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

- Nausea and vomiting.
- Breast tenderness or enlargement.
- 965 Enlargement of benign tumors ("fibroids") of the uterus.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face.

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970 **REDUCING RISK OF ESTROGEN USE**

If you use estrogens, you can reduce your risks by doing these things:

See your doctor regularly.

975 While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. 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.

980 *Reassess your need for estrogens.*

You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

Be alert for signs of trouble.

985 If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:

- Abnormal bleeding from the vagina (possible uterine cancer)
- Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)
- 990 • Severe headache or vomiting, dizziness, faintness, 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; ask your doctor or health professional to show you how to examine your breasts monthly)
- 995 • Yellowing of the skin or eyes (possible liver problem)
- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION

1000 1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormonal drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

1005 You should know, however, that taking estrogens *with* progestins may have additional risks. These may include unhealthy effects on blood fats (especially the lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease). However, while it has been reported that some estrogen and progestin combinations have an unfavorable effect on blood fats, studies of Premarin given with medroxyprogesterone acetate (MPA) (0.625 mg Premarin with either 2.5 mg MPA continuously or 5 mg of MPA cyclically) have shown decreases in LDL ("bad" cholesterol) and increases in HDL ("good" cholesterol). Other risks include unhealthy effects on blood sugars, which might make a diabetic condition worse, and a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

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1020 Some research has shown that estrogens taken *without* progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

1025 **You are cautioned to discuss very carefully with your doctor or health-care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.**

2. Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

1030 3. If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about the amounts recommended.

1035 4. Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.

1040 5. This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called *The Physicians' Desk Reference*, which is available in bookstores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

HOW SUPPLIED

Premarin® (conjugated estrogens tablets, USP) - tablets for oral administration.

- 1045 Each oval purple tablet contains 2.5 mg.
- Each oval yellow tablet contains 1.25 mg.
- Each oval white tablet contains 0.9 mg.
- Each oval maroon tablet contains 0.625 mg.
- 1050 Each oval blue tablet contains 0.45 mg.
- Each oval green tablet contains 0.3 mg.

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1055 **WYETH LOGO** Ayerst Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

CI 6032-5 Revised January 16, 2001

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WYETH #9406036 LABEL PREMARIN 0.3



NDC 0548-0888-01
0548-07-123-3171

100 Tablets

PREMARIN
conjugated estrogens tablets USP

ESTROGENS OBTAINED EXCLUSIVELY
FROM NATURAL SOURCES

0.3 mg

SEALED FOR YOUR PROTECTION

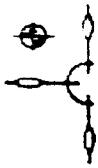
Caution: Please do not remove sealings without prescription

 Wyeth Laboratories Inc.
A Wyeth-Ayerst Company

Dispenser includes one "Information for the Patient" leaflet
with each package containing
Sixty six (66) individual tablets (approximately 25°C)
Dispensed in a small child-resistant container as directed on the USP

Each tablet contains 0.3 mg of conjugated estrogens
USP, in oral dosage form containing water-soluble
conjugated form
Usual Dosage: See accompanying prescribing literature
The appearance of these tablets is a trademark of
Wyeth-Ayerst Laboratories
Wyeth-Ayerst Laboratories Inc.
A Division of Wyeth-Ayerst Company
Philadelphia, PA 19101

Made and
printed in USA
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BLK GREEN

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■ BLACK

■ WCS 463

□ WCS 464

■ WCS 221

NDC 0046-0868-91 1,000
6505-00-003-5111 Tablets

Premarin®
(conjugated estrogens
tablets, USP)

ESTROGENS OBTAINED EXCLUSIVELY
FROM NATURAL SOURCES

0.3 mg

Note: Dispense in child-resistant packaging.
This package not for household use.

SEALED FOR YOUR PROTECTION

Caution: Federal law prohibits
dispensing without prescription.

 Ayerst Laboratories Inc.
A Wyeth-Ayerst Company



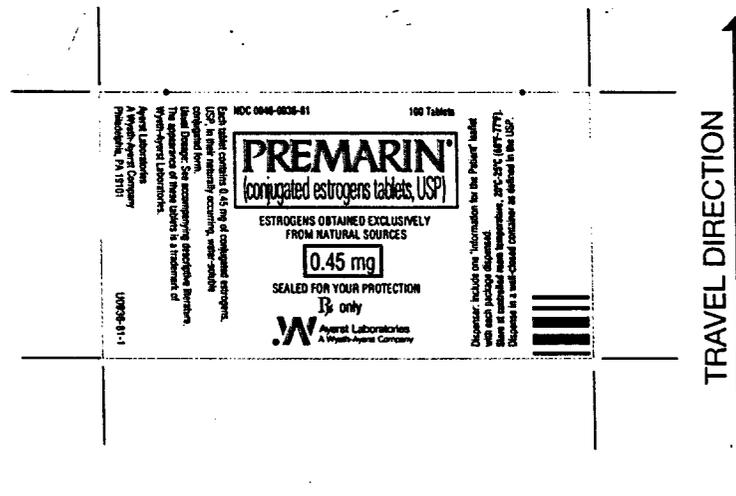
Dispenser: Include one
"Information for the Patient"
leaflet with each package
dispensed.
Store at room temperature
(approximately 25°C)
Dispense in a well-closed
container as defined in the
USP

Each tablet contains 0.3 mg of conjugated estrogens, USP,
in their naturally occurring, water-soluble conjugated form.
Usual Dosage: See accompanying descriptive literature.
The appearance of these tablets is a trademark of
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Philadelphia, PA 19101
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11-14-96 2P B**

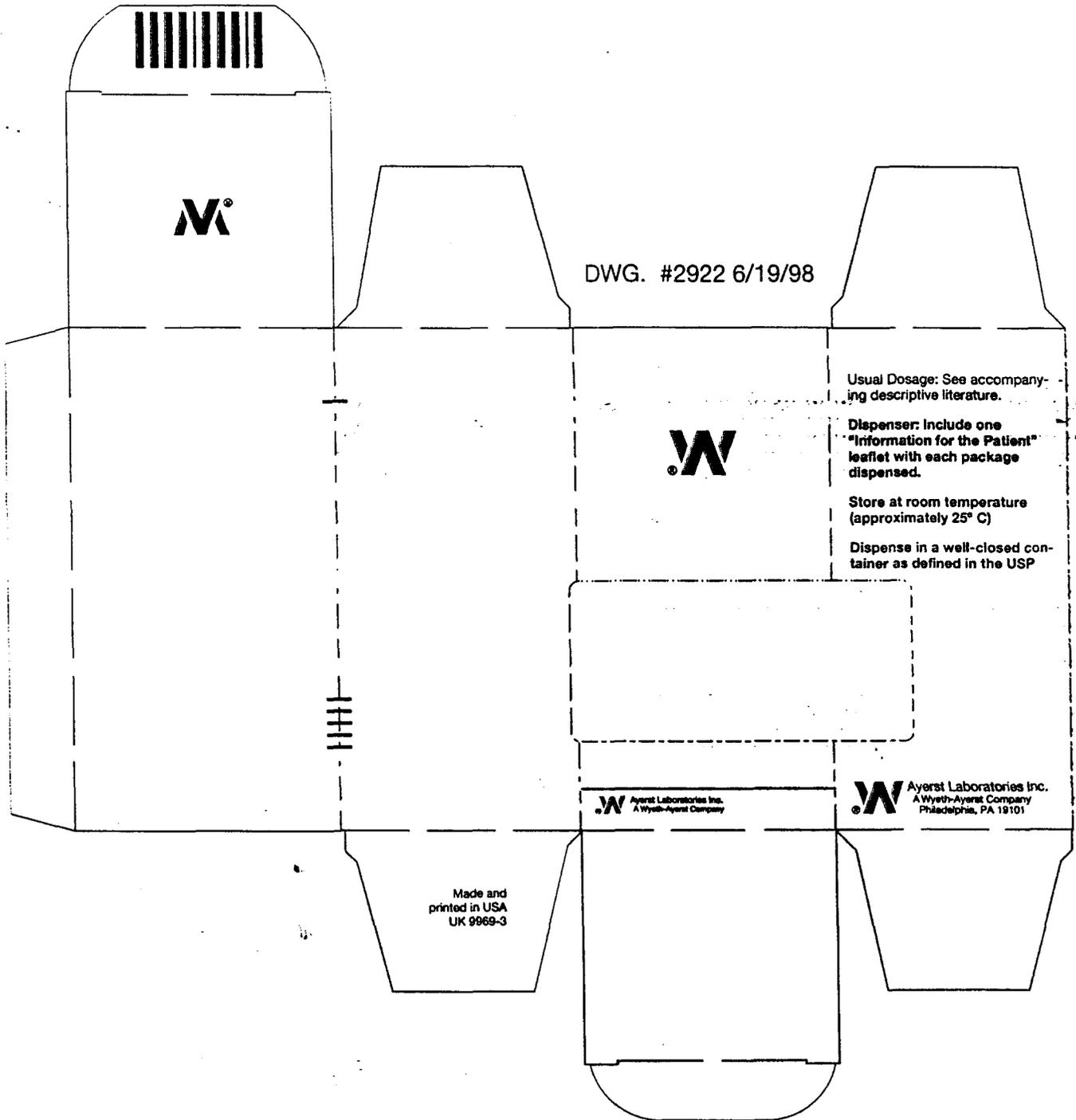
**PRINTER TO INSERT ACTUAL
UPC CODE AND NUMBER
N 0046-0868-91 3
AT SIZE AND POSITION SHOWN**

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2 3/4 x 1 1/2 inches Pharmacode 37
Black PMS 653 Dieline
SECOND PROOF



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UK 9969-3 Premarin for USA 1P 8.10.98 JSH
Black WCS 463 Dieline
45.5 x 42.5 x 89.5 W-A DWG. #2922, DATED 6/19/98
FIRST PROOF



remarin 0.3, 0.45 (Osteoporosis)

UK21103-2

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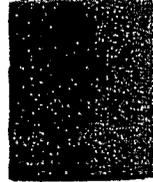
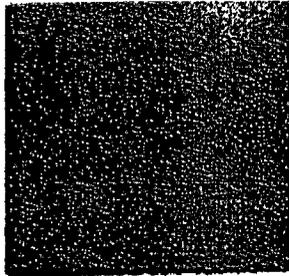
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Usual Dosage. See accompanying descriptive literature

Dispenser. Include one "Information for the Patient" leaflet with each package dispensed.

Store at room temperature (approximately 25° C)

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



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