2.1 Draft Package Insert (Unannotated)

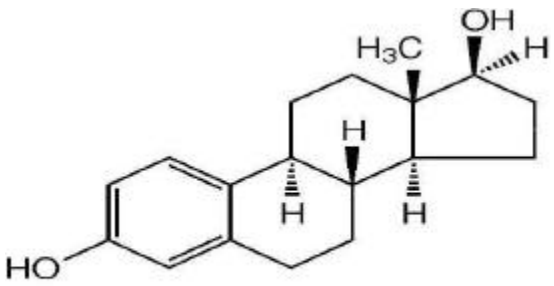
7-DAY ESTRADIOL TRANSDERMAL SYSTEM
PHYSICIANS LABELING

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 currently no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

DESCRIPTION

The TRADENAME transdermal system releases 17β-estradiol continuously upon application to intact skin. Estradiol USP (17β-estradiol) is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.37. The chemical structure is shown below.



TRADENAME is available in three sizes (13.5, 20, and 27 cm^2) with nominal in vivo delivery of 0.05, 0.075, and 0.1 mg, respectively, of 17$-estradiol per day continuously for 7 days via skin of average permeability. The total content of estradiol USP in the systems is 2.6 mg for the 13.5 cm^2, 3.9 mg for the 20 cm^2, and 5.3 mg for the 27 cm^2 systems.

The composition of the systems per unit area is identical.

TRADENAME has three layers as shown in the cross-sectional view below (not to scale).

1. Translucent flexible backing
2. Adhesive drug matrix layer
3. Metallic release liner to be removed

Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) the backing, a layer composed of a translucent coextruded polymeric barrier film that provides structural support and protects the middle layer from the environment, (2) the opaque middle adhesive/drug matrix layer that contains 17β-estradiol, acrylic adhesive, polyvinylpyrrolidone, and aluminum acetylacetonate, and (3) the release liner, a metallic film coated with silicone that protects the adhesive layer during storage and must be removed and discarded just before the system is applied. Release of estradiol from the system is primarily controlled by the adhesive, which ensures adhesion of the middle layer to the backing and of the product to the skin.

CLINICAL PHARMACOLOGY

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 μg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

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

Pharmacokinetics

TRADENAME produces mean serum concentrations of estradiol comparable with those produced by premenopausal women in the early follicular phase of the ovulatory cycle.

The pharmacokinetics of TRADENAME were evaluated in more than 100 healthy postmenopausal women in six clinical pharmacokinetic studies.

Absorption

Transdermal administration of estradiol produces therapeutic serum concentrations of estradiol with lower circulating concentrations of estrone and estrone conjugates and requires smaller total doses than does oral estradiol therapy.

The average daily dose absorbed from TRADENAME was 4.3 ± 1.5 µg of estradiol per cm^2 active surface area, based on analyses of the residual estradiol content in TRADENAME systems worn over a continuous 7-day interval in postmenopausal women. The 13.5 cm^2, 20 cm^2, and 27 cm^2 TRADENAME systems deliver approximately 0.05, 0.075, and 0.1 mg of estradiol per day.

In a multiple-dose, randomized, crossover study, 28 postmenopausal women were treated for 2 weeks with two of the three doses of TRADENAME (0.05, 0.075, or 0.1 mg/day). Each transdermal system was worn for 1 week (2 applications), with a 7- to 10-day washout period between doses. TRADENAME was applied to two sites on the abdomen. The pharmacokinetic parameters of serum estradiol are shown in Table 1 (unadjusted for baseline).

Table 1. PHARMACOKINETIC PARAMETERS OF TRADENAME, SERUM ESTRADIOL UNADJUSTED FOR BASELINE (MEAN ± SD)

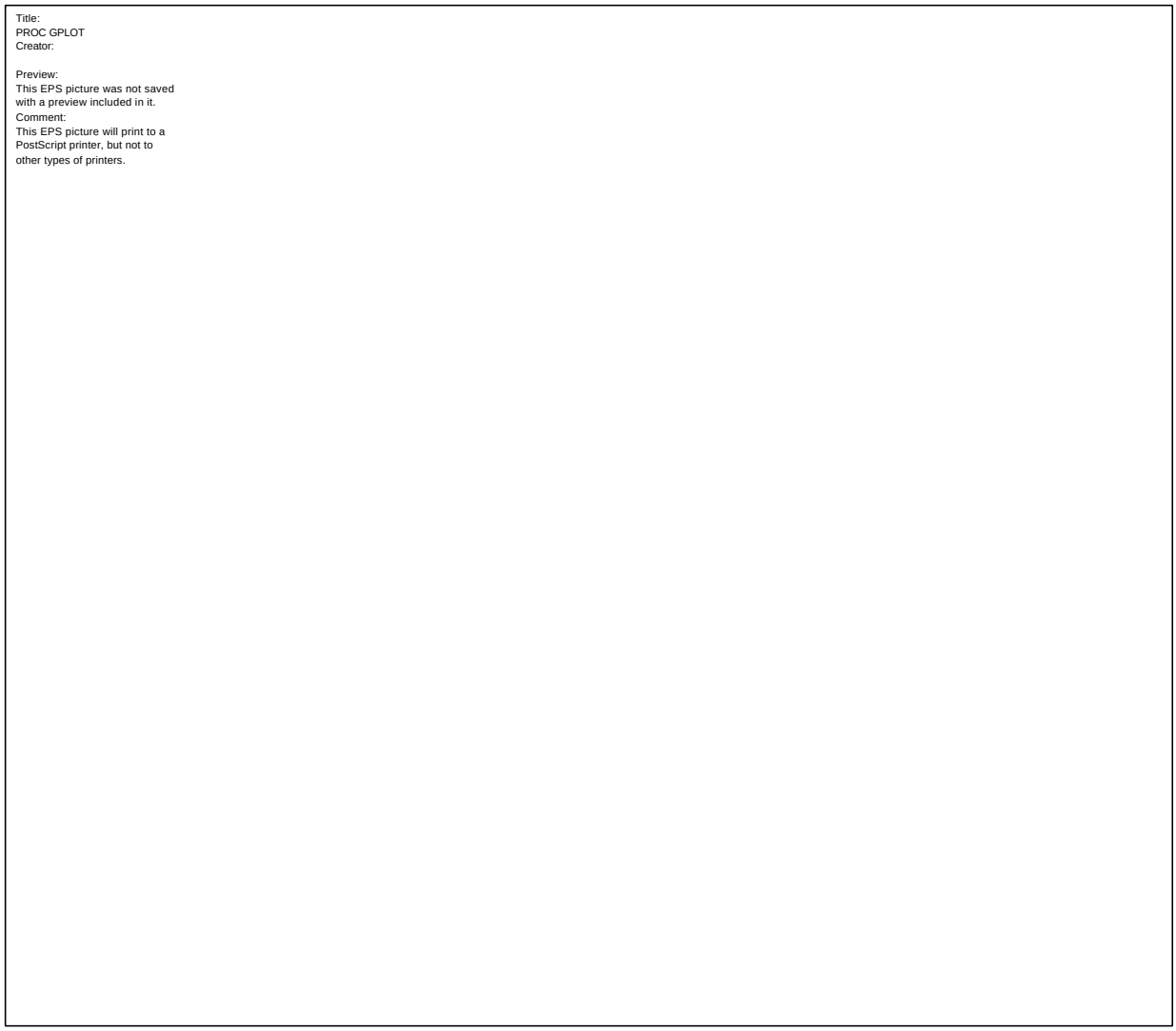
Treatment (mg/day)	Application Site	Week	C_{max} (pg/mL)	C_{avg} (pg/mL)	C_{min} [a] (pg/mL)
0.05	Abdomen	1	57 ± 36	39 ± 23	26 ± 15
		2	56 ± 34	37 ± 29	25 ± 24
0.075	Abdomen	1	72 ± 42	50 ± 29	33 ± 16
		2	87 ± 76	41 ± 20	23 ± 11
0.1	Abdomen	1	91 ± 32	62 ± 14	42 ± 13
		2	103 ± 40	60 ± 28	37 ± 33
0.1	Abdomen	1	105 ± 45	75 ± 25	-
	Hip	1	100 ± 40	70 ± 26	-
	Buttocks	1	112 ± 51	72 ± 28	-

a: C_{min} = concentration at time of TRADENAME removal.

The mean steady state serum estradiol concentration profiles with the application of TRADENAME patches delivering 0.05, 0.075, and 0.1 mg/day are shown in Figure 1.

Figure 1. MEAN SERUM ESTRADIOL CONCENTRATIONS UNADJUSTED FOR BASELINE LEVELS IN 28 HEALTHY POSTMENOPAUSAL WOMEN RECEIVING TRADENAME

■ 0.05 mg/day estradiol, week 1
9 0.05 mg/day estradiol, week 2
● 0.075 mg/day estradiol, week 1
O 0.075 mg/day estradiol, week 2
▲ 0.1 mg/day estradiol, week 1
❩ 0.1 mg/day estradiol, week 2
^ standard deviation



The relative bioavailability of TRADENAME at three different application sites was examined in a single-dose (0.1 mg/day) study with 36 healthy, hysterectomized, postmenopausal women. In this randomized, crossover study, patches were applied to the lower abdomen, the outer aspect of the hip, and the upper quadrant of the buttock. The pharmacokinetic parameters of serum estradiol (unadjusted for baseline levels) are shown in Table 1 and the mean serum concentration profiles are shown in Figure 2. There were no significant differences in pharmacokinetic parameters among the three application sites.

Figure 2. MEAN SERUM ESTRADIOL CONCENTRATIONS IN 36 HEALTHY POSTMENOPAUSAL WOMEN RECEIVING ONE 7-DAY APPLICATION OF TRADENAME (0.1 mg/day) APPLIED TO ABDOMEN, HIP, OR BUTTOCK

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone-binding globulin (SHBG), and to a lesser degree to 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.

Because transdermally absorbed estradiol is not subject to first-pass liver metabolism, the ratio of serum concentrations of estradiol to either of its major metabolites, estrone or estrone sulfate, is significantly greater than that seen for the oral route of administration. The mean ratio of estradiol to estrone was 1.3 for TRADENAME. The clinical relevance of the estradiol to estrone ratio is unknown.

The serum concentrations of estradiol and its metabolites were measured after 12 weeks of therapy (Table 2).

Table 2. SERUM CONCENTRATIONS OF ESTRADIOL AND ITS METABOLITES AFTER 12 WEEKS OF THERAPY WITH TRADENAME (pg/mL)

	0.05 mg/day		0.075 mg/day		0.1 mg/day	
Hormone	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Estradiol	58	41 ± 26	66	47 ± 36	70	67 ± 55
Estrone	58	41 ± 32	65	44 ± 19	69	52 ± 32
Estrone sulfate	58	592 ± 597	65	740 ± 523	69	850 ± 725

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Because estradiol has a short elimination half-life, transdermal administration of estradiol allows for rapid decline in blood levels after TRADENAME is removed.

Special Populations

TRADENAME has been studied only in postmenopausal women.

Race: No formal studies were done to evaluate the effect of race on the disposition of TRADENAME.

Hepatic Insufficiency: No formal studies were done to evaluate the effect of hepatic disease on the disposition of TRADENAME.

Renal Insufficiency: No formal studies were done to evaluate the effect of renal disease on the disposition of TRADENAME.

Drug-Drug Interactions: No specific drug interaction studies have been conducted using TRADENAME.

Adhesion

In two 12-week, double-blind, placebo-controlled studies, a total of 442 patients received 0.05, 0.075, or 0.1 mg/day TRADENAME. The percent adhesion of the patch at weeks 4, 8, and 12 was assessed. Among the TRADENAME recipients, 88% to 90% of the patches observed were 90% to 100% adherent. One patient in the 0.05 mg/day TRADENAME arm discontinued therapy during these clinical trials because of adhesion failure. In these trials, 4.1% (71/1730), 3.9% (74/1883) and 4.6% (83/1814) of the 0.05, 0.75 and 0.1 mg patches, respectively, required replacement due to inadequate adhesion.

CLINICAL STUDIES

In two 12-week, double-blind, placebo-controlled studies, a total of 442 postmenopausal women received TRADENAME (either 0.05, 0.075, or 0.1 mg per day) and 151 received placebo patches. On average, these patients had approximately 12 to 13 hot flushes per day upon study entry. After 4 weeks of treatment, all 3 TRADENAME groups showed a significantly greater reduction in the mean daily number and severity of hot flushes vs. placebo. Results from weeks 4, 8, and 12 of these trials are shown in Figures 3 and 4.

Figure 3. Mean changes in daily number of hot flushes in study 1 (intent-to-treat population). Treatment groups: TRADENAME 0.05, 0.075, and 0.1 mg/day, and placebo patches; n = number of subjects randomized to each treatment group.

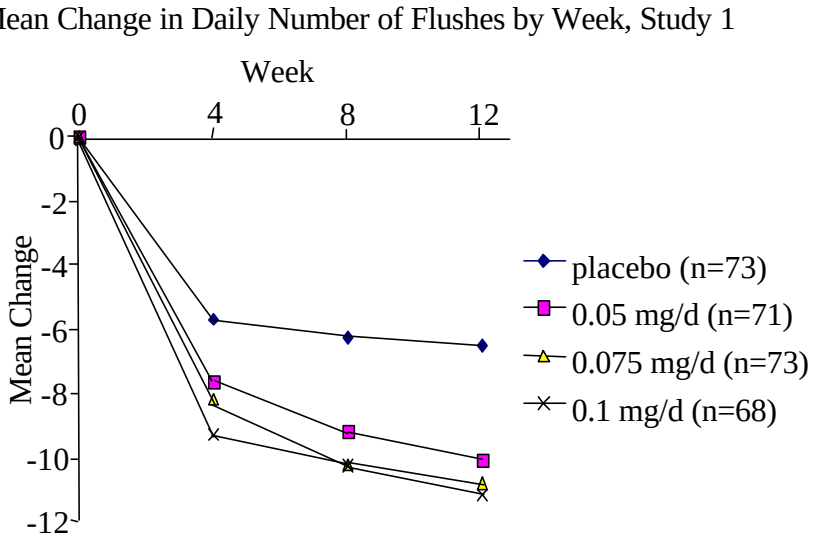
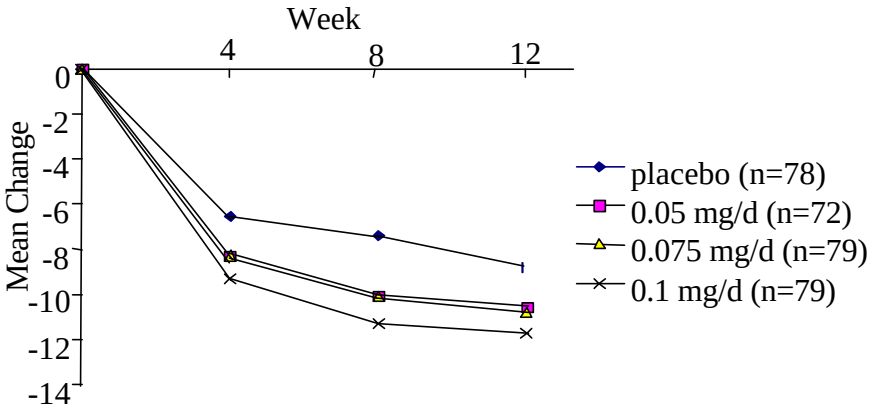


Figure 4. Mean changes in daily number of hot flushes in study 2 (intent-to-treat population). Treatment groups: TRADENAME 0.05, 0.075, and 0.1 mg/day, and placebo patches; n = number of subjects randomized to each treatment group.



INDICATIONS

TRADENAME (estradiol transdermal system) is indicated for the following:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.

CONTRAINDICATIONS

Patients with known hypersensitivity to any of the components of the therapeutic system should not use TRADENAME. Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see PRECAUTIONS). Estrogen may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast.
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders or a history of these conditions in association with previous estrogen use.
6. TRADENAME should not be used in patients hypersensitive to its ingredients.

WARNINGS

1. INDUCTION OF MALIGNANT NEOPLASMS

Endometrial Cancer

The reported uterine 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 1 year. The greatest risk appears associated with prolonged use--with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after cessation of estrogen treatment. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

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.

2. GALLBLADDER DISEASE

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

3. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

In some studies, women on estrogen replacement therapy, given alone or in combination with a progestin, have been reported to have an increased risk of thrombophlebitis and/or thromboembolic disease. The physician should be aware of the possibility of thrombotic disorders (including 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 monitored.

4. CARDIOVASCULAR DISEASE

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.

5. HYPERCALCEMIA

Administration of estrogens 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 should be 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 significantly reduced incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphologic 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 that may be associated with the use of progestins in estrogen replacement regimens. These include:

(1) adverse effects on lipoprotein metabolism, such as, lowering high-density lipoprotein (HDL) and raising low-density lipoprotein (LDL), which could diminish the purported cardioprotective effect of estrogen therapy (see PRECAUTIONS, below);

(2) impairment of glucose tolerance; and

(3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiologic 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.

2. CARDIOVASCULAR RISK

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.

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 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, the apparently reduced risk of cardiovascular 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 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.

(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 levels.

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

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women with a uterus who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential

benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

3. 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 with nonusers. Blood pressure should be monitored at regular intervals during estrogen use. Transdermally administered estradiol has not been reported to affect renin substrate.

4. PHYSICAL EXAMINATION

A complete medical and family history should be taken before 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 be prescribed for no longer than 1 year without another physical examination being performed.

5. 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 increased coagulation parameters at baseline compared with premenopausal women. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

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.

7. FLUID RETENTION

Because estrogens may cause some degree of fluid retention, careful observation is required when conditions that might be exacerbated by this factor are present (eg, asthma, epilepsy, migraine, and cardiac or renal dysfunction).

8. UTERINE BLEEDING AND MASTODYNIA

Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

9. IMPAIRED LIVER FUNCTION

Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients.

10. UTERINE FIBROIDS

Preexisting uterine leiomyomata may increase in size during estrogen use.

11. HYPOCALCEMIA

Estrogens should be used with caution in individuals with metabolic bone disease associated with severe hypocalcemia.

B. INFORMATION FOR THE PATIENT

See text of Patient Package Insert, which appears after the HOW SUPPLIED section.

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.

D. DRUG/LABORATORY TEST INTERACTIONS

Estrogen has been found to influence laboratory values in the following ways.

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 β-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, 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.

3. Other binding proteins may be elevated in serum, eg, corticosteroid-binding globulin (CBG) and 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, α1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL_2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides 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). 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 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. Although some of these changes are benign, others are precursors of malignancy.

F. PREGNANCY CATEGORY X

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.

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.

G. NURSING MOTHERS

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary because 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.

ADVERSE REACTIONS

In two 12-week, double-blind, placebo-controlled studies, a total of 442 patients received TRADENAME (either 0.05, 0.075, or 0.1 mg per day) and 151 patients received placebo patches. Treatment-emergent adverse reactions that occurred in 3% or more of the patients in any treatment group are shown in Table 4. The most commonly reported adverse reactions with use of TRADENAME were headache, breast pain, and application site reactions.

Table 4. COMMONLY REPORTED (≥ 3%) TREATMENT-EMERGENT ADVERSE EVENTS IN TWO DOUBLE-BLIND CLINICAL STUDIES, % OF PATIENTS[a]

Body system Adverse event	0.05 mg/day (n = 143)	0.075 mg/day (n = 152)	0.1 mg/day (n = 147)	Placebo (n = 151)
Body as a whole				
Abdominal pain	6	6	12	5
Accidental injury	6	2	5	2
Asthenia	6	2	3	3
Back pain	4	8	5	7
Flu syndrome	5	5	5	5
Headache	23	18	20	16
Infection	5	9	4	3
Pain	11	9	7	6
Digestive system				
Diarrhea	5	1	2	4
Dyspepsia	2	3	<1	3
Flatulence	5	2	7	2
Nausea	8	7	8	2
Metabolic and nutritional				
Peripheral edema	3	3	2	<1
Musculoskeletal system				
Arthralgia	4	3	4	3
Nervous system				
Depression	1	3	3	2
Emotional lability	3	1	5	<1
Insomnia	3	2	5	7
Respiratory system				
Cough increased	3	0	1	2
Pharyngitis	7	3	10	10
Rhinitis	5	1	5	3
Sinusitis	3	1	3	2
Skin and appendages				
Acne	3	2	2	1
Application site reaction	11	11	15	8
Pruritus	3	5	5	3
Rash	2	5	4	3
Urogenital system				
Breast pain	12	18	24	3
Leukorrhea	5	5	3	0
Vaginal hemorrhage	2	3	3	1

a: 3% or more in any one treatment group

Of the application site reactions that occurred in the two double-blind studies, 45% consisted of mild itching and erythema. Three (<1%) patients treated with TRADENAME (all with the 0.1 mg/day patch) withdrew from these clinical studies because of rashes or other skin reactions at the application site. One (0.7%) placebo recipient also withdrew prematurely because of an application site reaction.

The following additional adverse reactions have been reported with estrogen therapy (see WARNINGS regarding induction of neoplasia, adverse effects on the fetus, increased

incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia).

1. GENITOURINARY SYSTEM

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; increase in size of uterine leiomyomata; vaginal candidiasis; change in amount of cervical secretion.

2. BREASTS

Tenderness; enlargement.

3. GASTROINTESTINAL

Nausea; vomiting; abdominal cramps; bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis.

4. CARDIOVASCULAR

Venous thromboembolism; pulmonary embolism.

5. SKIN

Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.

6. EYES

Steepening of corneal curvature; intolerance to contact lenses.

7. CENTRAL NERVOUS SYSTEM

Headache; migraine; dizziness; mental depression; chorea.

8. MISCELLANEOUS

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

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

DOSAGE

For the treatment of moderate to severe vasomotor symptoms, and vulvar and vaginal atrophy associated with the menopause, treatment is generally initiated with the

TRADENAME 0.05 mg transdermal system applied to the skin once weekly. There are three TRADENAME dosages available with nominal delivery of 0.05, 0.075, and 0.1 mg/day of estradiol. The lowest dosage that effectively controls symptoms should be used. The dosage should be adjusted as necessary to control symptoms. Attempts to taper or discontinue the medication should be made at 3- to 6-month intervals.

In women who are not currently taking oral estrogens, treatment with TRADENAME can be initiated at once. In women who are currently taking oral estrogen, treatment with TRADENAME can be initiated 1 week after withdrawal of oral therapy or sooner if symptoms reappear in less than 1 week.

ADMINISTRATION

The adhesive side of the TRADENAME system should be placed on a clean, dry area of the skin on the trunk of the body (including the buttocks, hip, or abdomen). The area selected should not be oily, damaged, or irritated. TRADENAME should be under clothing; however, the waistline should be avoided, because clothing may rub the system off. TRADENAME should not be applied on or near the breasts.

TRADENAME should be replaced once weekly. The sites of application must be rotated, with an interval of at least 1 week between applications to a particular site. Apply TRADENAME immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the hand for about 10 seconds, making sure there is good contact, especially around the edges.

Transdermal systems should not be taken off during normal baths, showers or swimming. If TRADENAME falls off, the same system may be reapplied or a new patch may be applied. In either case, the original treatment schedule should be continued.

THERAPEUTIC REGIMEN

TRADENAME may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, TRADENAME may be given continuously or on a cyclic schedule (e.g., 3 weeks on drug followed by 1 week off drug). In patients with an intact uterus, concomitant progestin therapy is recommended (see PRECAUTIONS).

HOW SUPPLIED

Each 13.5-cm^2 TRADENAME contains 2.6 mg estradiol USP for nominal delivery of 0.05 mg of estradiol per day for 7 days.
NDC..

Each 20-cm^2 TRADENAME contains 3.9 mg estradiol USP for nominal delivery of 0.075 mg of estradiol per day for 7 days.
NDC...

Each 27-cm^2 TRADENAME contains 5.3 mg estradiol USP for nominal delivery of 0.1 mg of estradiol per day for 7 days.
NDC...

Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F)
(See USP Controlled Room Temperature)
Rx only

Do not store unpouched. Apply immediately upon removal from the protective pouch. Discard used TRADENAME in household trash in a manner that prevents accidental application or ingestion by children, pets, or others.

Manufactured by: Cygnus, Redwood City, CA 94063
For: Wyeth-Ayerst, Philadelphia, PA
Date:

7-DAY ESTRADIOL TRANSDERMAL SYSTEM

PATIENT PACKAGE INSERT:
INFORMATION FOR THE PATIENT
INTRODUCTION

This leaflet describes when and how to use TRADENAME and the benefits and risks of estrogen treatment. TRADENAME is an estradiol patch (sometimes called an estradiol transdermal system). Your health care provider has prescribed the TRADENAME estradiol patch for the treatment of your menopausal symptoms. Estradiol is the same hormone that your ovaries produce before menopause. During menopause, production of estrogen hormones by your body decreases below the amounts normally produced during your fertile years. In many women this decrease in estrogen production causes uncomfortable symptoms, most noticeably hot flushes and related sleep disturbances, and vaginal dryness. TRADENAME can be used to reduce or eliminate these symptoms.

Estrogens have important benefits but also some risks. You must decide, with your health care provider, whether the benefits of estrogen use outweigh the risks. If you use estrogens, check with your health care provider to be sure you are using the lowest possible dose that works and that you don't use them longer than necessary. How long you need to use estrogens will depend on the reason for use.

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 health care provider regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your health care provider should evaluate any unusual vaginal bleeding to find out the cause.

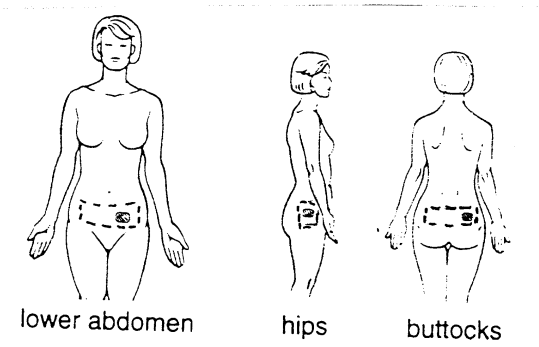
INFORMATION ABOUT TRADENAME
How TRADENAME Works

TRADENAME releases small amounts of estradiol through the skin and into the blood stream in a continuous way. The dose of estradiol you require will depend upon your individual response. The dose is adjusted by the size of the TRADENAME. There are three sizes of TRADENAME available.

HOW, WHERE, AND WHEN TO APPLY TRADENAME

Read through the following instructions before applying the TRADENAME**.**

The following figure shows sites where the patch can be placed (broken lines (------) designate allowable area for placement, solid line rectangles designate preferred placement sites.)



Each TRADENAME is individually sealed in a protective pouch. Tear open this pouch at the indentation (do not use scissors) and remove the patch. A protective silver metallic liner covers the adhesive side of the patch--the side that will be placed against your skin. This liner must be removed before applying the patch. Apply TRADENAME immediately after opening the pouch and removing the protective liner.

Use the following procedure when applying TRADENAME.

- With the silver side facing you, hold the patch by the corner.
- Bend the patch slightly to separate the 2 edges of the cut, and peel away a portion of the silver protective liner and discard it. Try to avoid touching the adhesive.
- Holding the patch on the side where the liner remains, apply the patch to a clean, dry area of the skin on the lower abdomen, buttocks, or hip. **Do Not Apply TRADENAME On or Near Your Breasts**. The area selected should not be oily, hairy, damaged, or irritated. Wear the patch under clothing but avoid the waistline because clothing could rub and remove the patch.
- Remove the remaining portion of the liner and press the patch firmly in place with your hand for about 10 seconds, making sure there is good contact, especially around the edges.

The TRADENAME should be worn continuously for 1 week. Changing the patch at the same time on the same day each week may make it easier to remember your schedule. After 1 week of use, remove the patch and discard it in household trash in a manner that prevents accidental application or ingestion by children, pets, or others. Then immediately apply a new patch to a different site on the lower abdomen, buttocks, or hip. There should be an interval of at least 1 week between applications to a particular site. Only one patch should be worn at any time.

TRADENAME should not be taken off during normal baths, showers, or swimming. If TRADENAME falls off, the same patch may be reapplied or a new patch may be applied. In either case, the original treatment schedule should be continued.

If you forget to remove or apply a patch on the required day, change it when you remember. Even if a patch is applied after the scheduled day, you should still remove it and replace it on the next regularly scheduled day. Always return to your original schedule as soon as possible. For example, if you forget to remove a patch on Saturday morning, but remember it on Sunday, remove it and apply a new one on Sunday. If your day to change the patch is Saturday, apply a new patch the following Saturday after removing the old one, and maintain your original day for patch change.

USES OF ESTROGEN

-- To reduce moderate-to-severe menopausal symptoms

Estrogens are hormones produced by the ovaries. The decrease in the amount of estrogen that occurs in women, usually between ages 45 and 55, causes menopause. Sometimes the ovaries are removed by an operation, causing "surgical menopause." When the amount of estrogen begins to decrease, 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 flushes"). The use of drugs containing estrogens can help the body adjust to lower estrogen levels. Some women have only mild menopausal symptoms, or none at all, and do not need estrogen therapy for these particular symptoms. Other women may need estrogens for varying periods of time while their bodies adjust to lower estrogen levels. For the treatment of menopausal symptoms only, most women need estrogen replacement therapy for no longer than 6 months. Because every woman is different, you and your health care provider should periodically reevaluate your need for continued estrogen use.

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

WHO SHOULD NOT USE ESTROGENS

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.

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.

-- IF YOU HAVE UNUSUAL VAGINAL BLEEDING WHICH HAS NOT BEEN EVALUATED BY YOUR HEALTH CARE PROVIDER (SEE BOXED WARNING)

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

-- IF YOU HAVE HAD CANCER

Because 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 health care provider recommends that the drug may help in the cancer treatment.

-- IF YOU HAVE ANY CIRCULATION PROBLEMS

Estrogen drugs should not be used except in special situations in which your health care provider 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).

-- AFTER CHILDBIRTH OR WHEN BREASTFEEDING A BABY

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).

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

The risk of developing cancer of the uterus gets higher the longer estrogens are used and when larger doses are taken. One study showed that when estrogens are discontinued, this increased risk of cancer seems to fall off quickly. Three other studies showed that the risk for uterine cancer stayed high for 8 to 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.**

Using progestin therapy together with estrogen therapy reduces the higher risk of uterine cancer related to estrogen use (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

Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods. Regular breast examinations by a health professional and monthly self-examination are recommended for all women. Yearly mammography is recommended for women as appropriate for their age.

-- GALLBLADDER DISEASE

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

-- ABNORMAL BLOOD CLOTTING

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 (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long-term disability.

-- SIDE EFFECTS

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

-- Headache.
-- Nausea and vomiting.
-- Breast tenderness or enlargement.
-- 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.
-- Women with increased triglyceride levels may have an increased risk of developing inflammation of the pancreas.
-- A spotty darkening of the skin, particularly on the face, which may persist when drug is discontinued.
-- With estrogen patch use, skin irritation, redness, or rash may occur at the site of patch application.

REDUCING RISK OF ESTROGEN USE

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

-- SEE YOUR HEALTH CARE PROVIDER REGULARLY

While you are using estrogens, it is important to visit your health care provider 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.

-- REASSESS YOUR NEED FOR ESTROGENS

You and your health care provider should reevaluate whether or not you still need estrogens at least every 6 months.

-- BE ALERT FOR SIGNS OF TROUBLE

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 (indicating possible clots in the legs, heart, or lungs).
-- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (indicating possible clots in the brain or eye).
-- Breast lumps (possible breast cancer - ask your doctor or health professional to show you how to examine your breasts monthly).
-- Yellowing of the skin or eyes (possible liver problem).
-- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem).
-- Persistent, severe skin irritation, redness, or rash (possible allergic reaction).

OTHER INFORMATION

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 hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your health care provider may prescribe a progestin for you to take together with your estrogen. You should know, however, that taking estrogens with progestins may have additional risks. These include:

-- unhealthy effects on blood fats (especially a lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease);
-- unhealthy effects on blood sugar (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.

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.

You Are Cautioned To Discuss Very Carefully With Your Health Care Provider All The Possible Risks And Benefits Of Long-term Estrogen And Progestin Treatment As They Affect You Personally

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

3. Keep this and all drugs out of the reach of children. In case of overdose, call your health care provider, hospital or poison control center immediately.

4. This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your health care provider 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.

STORAGE
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