CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020994, 020375/S011

Trade Name: CLIMARA

Generic Name: ESTRADIOL TRANSDERMAL SYSTEM

Sponsor: BERLEX LABORATORIES, INC

Approval Date: 3/5/99

Indication(s): THE PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

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APPLICATION: 020994, 020375/S011

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Application Number: 020994, 020375/S011

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-994
NDA 20-375/S-011

MAR 5 1999

Berlex Laboratories, Inc.
Attention: Mr. Geoffrey Millington
Manager
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045

Dear Mr. Millington:

Please refer to your new drug application (NDA) dated May 1, 1998, received May 5, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara (estradiol transdermal system), 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

We also refer to your supplemental new drug application, Supplement - 011 submitted to NDA 20-375 Climara (estradiol transdermal system) on May 1, 1998, and received May 5, 1998.

We acknowledge receipt of your submissions dated June 18, July 16, and December 7, 1998; January 5, 12, 15, 21, and 25, February 2, 4, 9, 16, and 24, and March 4, 1999, to NDA 20-994. We also acknowledge receipt of your submissions dated May 12, 1998, and March 4, 1999, to NDA 20-375/S-011.

This new drug application provides for a new indication, the prevention of postmenopausal osteoporosis (loss of bone mass), for the previously approved strengths of Climara, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day, and for a new lower strength, 0.025 mg/day, which is added in this application.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft labeling. Accordingly, the applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician package insert and patient package insert dated March 4, 1999, and immediate container and carton labels submitted May 1, 1998. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit to the Division of Reproductive and Urologic Drug Products, HFD-580, Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857, 20 copies of the FPL as

soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-375/S-011." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Reproductive and Urologic Drug Products, HFD-580, and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available to NDA 20-375/S-011.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. To comply with these regulations, all 7-day and 15-day alert reports, periodic adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 20-375, for this drug product, not to this NDA. This includes the quarterly periodic adverse drug experience reports required by this new NDA. In the future, no submissions should be made to this NDA.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020994, 020375/S011

FINAL PRINTED LABELING

PRESCRIBING INFORMATION **Climara® estradiol transdermal system**

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

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY
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.

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.

DESCRIPTION

Climara®, estradiol transdermal system, is designed to release 17β-estradiol continuously upon application to intact skin. Four (6.5, 12.5, 18.75 and 25.0 cm^2) systems are available to provide nominal *in vivo* delivery of 0.025, 0.05, 0.075 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 12.5, 18.75 or 25.0 cm^2, and contains 2.04, 3.9, 5.85 or 7.8 mg of estradiol USP respectively. The composition of the systems per unit area is identical.

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 structural formula is:

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The Climara® system comprises two layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film, and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the system can be used.

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The active component of the system is 17β-estradiol. The remaining components of the system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

The Climara® system provides systemic estrogen replacement therapy by releasing 17β-estradiol, the major estrogenic hormone secreted by the human ovary.

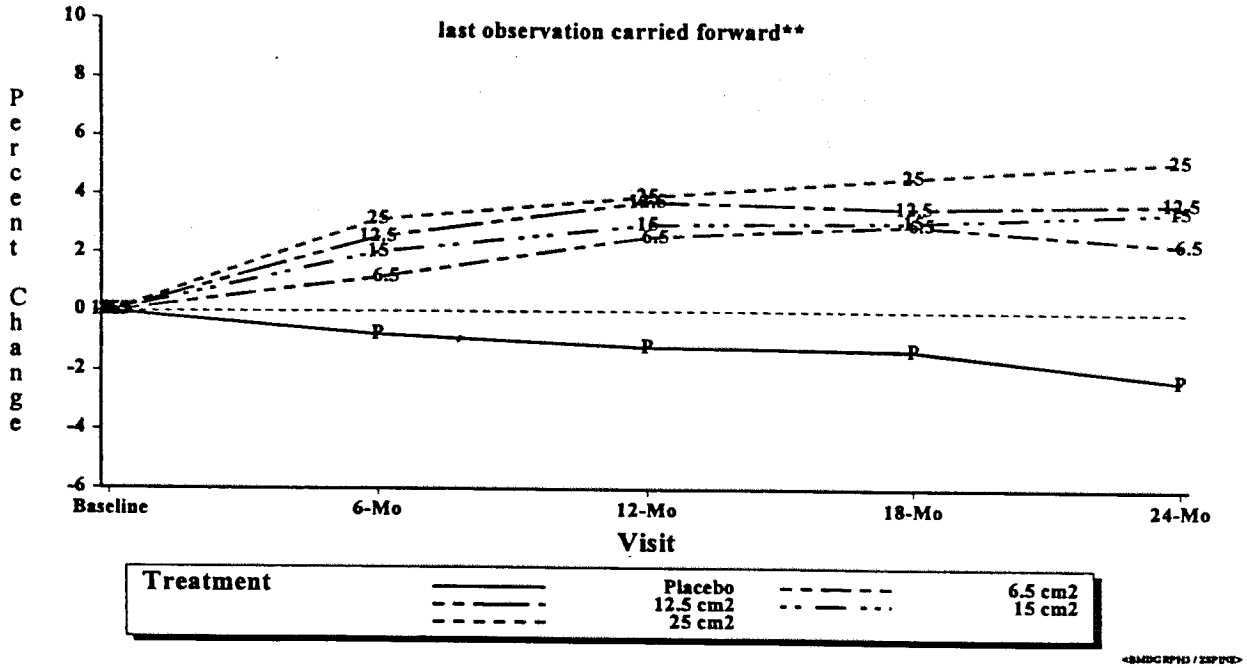
Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially 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. luteininizing hormone (LH) and follicle stimulating hormone (FSH) through negative feedback mechanism and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

A two-year clinical trial enrolled a total of 175 healthy, hysterectomized, postmenopausal, non-osteoporotic (i.e., lumbar spine bone mineral denstiy > 0.9 gm/cm^2) women at 10 study centers in the United States[8]. 129 subjects were allocated to receive active treatment with 4 different doses of 17 β-estradiol patches (6.5, 12.5, 15, 25 cm^2) and 46 subjects were allocated to receive placebo patches. 77% of the randomized subjects (100 on active drug and 34 on placebo) contributed data to the analysis of percent change of A-P spine bone mineral density (BMD), the primary efficacy variable (see Figure 1). A statistically significant overall treatment effect at each timepoint was noted, implying bone preservation for all active treatment groups at all timepoints, as opposed to bone loss for placebo at all timepoints.

Figure 1. Mean Percent change from Baseline in Lumbar Spine (A-P View) Bone Mineral Density By Treatment and Time

last observation carried forward**

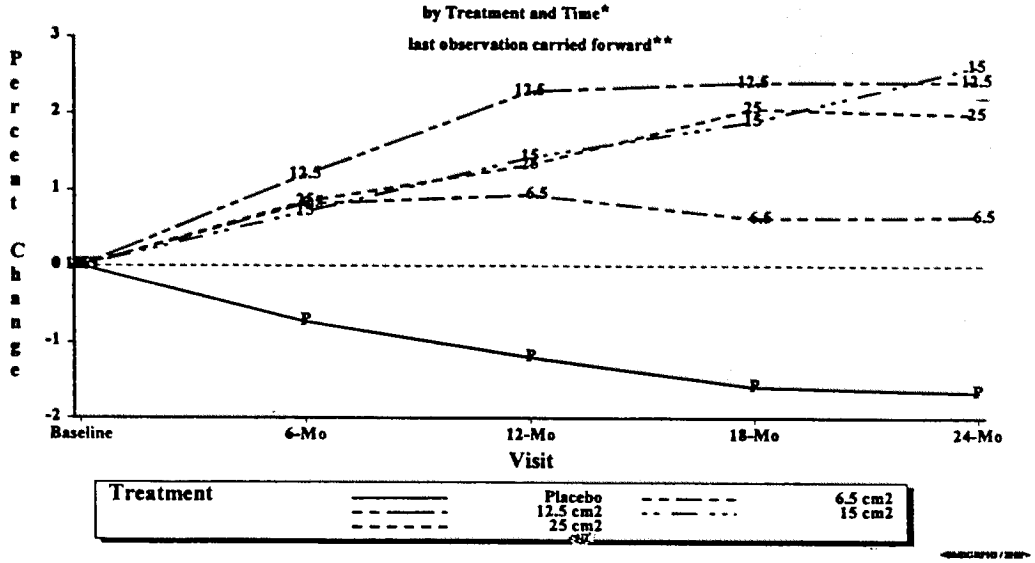


Please note that the ordinat scale for figures 1 and 2 will be revised to a range of +6 to –6.

Percent change in BMD of the total hip (see Figure 2), was also statistically significantly different from placebo for all active treatment groups. The results of the measurements of biochemical markers supported the finding of efficacy for all doses of transdermal estradiol. Serum osteocalcin levels decreased, indicative of a decrease in bone formation, at all timepoints for all active

treatment doses, statistically significantly different from placebo (which generally rose). Urinary deoxypyridinoline and pyridinoline changes also suggested a decrease in bone turnover for all active treatment groups.

Figure 2. Mean Perecent Change from Baseline in Total Hip by Treatment and Time*
last observation carried forward**



Footnote: This figure is based on 74% of the randomized subjects (95 on active drug and 34 on placebo).

PHARMACOKINETICS

Transdermal administration of Climara® produces mean serum concentrations of estradiol comparable to those produced by premenopausal women in the early follicular phase of the ovulatory cycle. The pharmacokinetics of estradiol following application of the Climara® system were investigated in 197 healthy postmenopausal women in six studies. In five of the studies Climara® system was applied to the abdomen and in a sixth study application to the buttocks and abdomen were compared.

Absorption: The Climara® transdermal delivery system continuously releases estradiol which is transported across intact skin leading to sustained circulating levels of estradiol during 7 day treatment period. The systemic availability of estradiol after transdermal administration is about 20 times higher than that after oral administration. This difference is due to the absence of first pass metabolism when estradiol is given by the transdermal route.

The bioavailability of Climara® was determined in two single dose studies after 1 week application of the Climara® system versus two consecutive 3 day and 4 day applications of the Estraderm® system. Mean estradiol serum concentrations observed during the treatment of the 25.0 and 12.5

cm^2 Climara® systems versus the 20 and 10 cm^2 Estraderm® systems are shown in Figures 3 and 4, respectively. Both sizes of Climara® maintained significantly lower peak and mean steady state estradiol levels than did the Estraderm® system; however, towards the end of each treatment period, the Climara® system maintained similar (day 6) or higher (day 7) serum estradiol levels than did the Estraderm® system. The fluctuation index with the Climara® system was ¼ to 1/3 the fluctuation index observed with Estraderm®. However, this has not been shown to be clinically significant.

Figure 3
Observed Mean (± S.E.) Estradiol Serum Concentrations for a One Week Application of the Climara® system (25 cm^2) and Consecutive Three Day and Four Day Application of the Estraderm® System (20 cm^2) in 24 postmenopausal women

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Figure 4
Observed Mean (± S.E.) Estradiol Serum Concentrations for a One Week Application of the Climara® system (12.5 cm^2) and Consecutive Three Day and Four Day Application of the Estraderm® System (10 cm^2) in 24 postmenopausal women

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In a third bioavailability study, the Climara 6.5 cm^2 was studied with the Climara 12.5 cm^2 as reference. The mean estradiol levels in serum from the 2 sizes are shown in Figure 5.

Figure 5
Mean Serum 17β-Estradiol Concentrations vs. Time Profile following Application of a 6.5 cm^2 Transdermal Patch and Application of a 12.5 cm^2 Climara patch.

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Time in (hrs)

Legend: O 6.5 cm^2 Climara patch
□ 12.5 cm^2 Climara patch

Dose proportionality was demonstrated for the Climara 6.5 cm^2 patch as compared to the Climara 12.5 cm^2 patch in a 2 week crossover study with a one week washout period between the two patches in 24 postmenopausal women.

Dose proportionality was also demonstrated for the Climara® system (12.5 cm^2 and 25 cm^2) in a 1week study conducted in 54 postmenopausal women. The mean steady state levels (Cavg) of the estradiol during the application of Climara 25 cm^2 and 12.5 cm^2 on the abdomen were about 80 and 40 pg/mL, respectively.

In a 3 week multiple application study in 24 postmenopausal women, the 25.0 sq cm Climara® system produced average peak estradiol concentrations (Cmax) of approximately 100 pg/mL. Trough values at the end of each wear interval (Cmin) were approximately 35 pg/mL. Nearly identical serum curves were seen each week, indicating little or no accumulation of estradiol in the body. Serum estrone peak and trough levels were 60 and 40 pg/mL, respectively.

In a single dose randomized crossover study conducted to compare the effect of site of application, 38 postmenopausal women wore a single Climara® 25 sq cm system for 1 week on the abdomen and buttocks. The estradiol serum concentration profiles are shown in Figure 6. Cmax and Cavg values were, respectively, 25% and 17% higher with the buttock application than with the abdomen application.

Figure 6.
Observed Mean (± S.E.) Estradiol Serum Concentrations for a One Week Application of the Climara® system (25 cm^2) to the abdomen and buttocks of 38 postmenopausal women.

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Table 1 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of Climara®.

Table 1
Pharmacokinetic Summary
(Mean Estradiol Values)

Climara® Delivery Rate	Surface Area (cm^2)	Application Site	No. of Subjects	Dosing	Cmax (pg/mL)	Cmin (pg/mL)	Cavg (pg/mL)
0.025	6.5	Abdomen	24	Single	32	17	22
0.05	12.5	Abdomen	102	Single	71	29	41
0.1	25	Abdomen	139	Single	147	60	87
0.1	25	Buttock	38	Single	174	71	106

The relative standard deviation of each pharmacokinetic parameter after application to the abdomen averaged 50%, which is indicative of the considerable intersubject variability associated with transdermal drug delivery. The relative standard deviation of each pharmacokinetic parameter after application to the buttock was lower than that after application to the abdomen (e.g., for Cmax 39% vs 62%, and for Cavg 35% vs 48%).

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 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.

Excretion: Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. After removal of the Climara® system, serum estradiol levels decline in about 12 hours to preapplication levels with an apparent half life of approximately 4 hours.

Special populations:

Race: There is no available information to establish the relevance of race for the absorption and pharmacokinetics of estradiol following transdermal application.

Patients with Renal Impairment: Total estradiol serum levels are higher in postmenopausal women with end stage renal disease (ESRD) receiving maintenance hemodialysis than in normal subjects at baseline and following oral doses of estradiol. Therefore, conventional transdermal estradiol doses used in individuals with normal renal function may be excessive for postmenopausal women with ESRD receiving maintenance hemodialysis.

Patients with Hepatic Impairment: Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

INDICATIONS AND USAGE

Climara® is indicated in the:

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

3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

4. Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium.

5. Prevention of Postmenopausal Osteoporosis (loss of bone mass). The mainstays of prevention of postmenopausal osteoporosis are estrogen, an adequate lifetime calcium and vitamin D intake, and exercise.

Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-controlled studies have shown an approximately 60% 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 treatment is continued. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period.

CONTRAINDICATIONS

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

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 thrombophlebitis or thromboembolic disorders.

WARNINGS

1. **Induction of malignant neoplasms.**

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. 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, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years.

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.

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.

3. **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. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

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. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use. Ethinyl estradiol and conjugated estrogens have been shown to increase renin substrate. In contrast to these oral estrogens, transdermally administered estradiol has been reported not to affect renin substrate.

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 that may be associated with the use of progestins in estrogen replacement regimens. These include: (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL) which could diminish the purported cardioprotective effect of estrogen therapy (see Precautions D.4., below); (2) impairment of glucose tolerance; and (3) 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**. *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 that 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 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 a 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. (2) Current medical practice often includes the use of concomitant progestin therapy 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 epidemiological 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 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. **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.

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 increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogens users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

5. **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.

6. **Fluid retention**. Because estrogens may cause some degree of fluid retention, conditions that might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

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

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

B. **Information for the Patient**. See text of Patient Package Insert 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**.

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 betathromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), 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, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 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, and Impairment of Fertility**. See Contraindications and Warnings. 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.

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

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

ADVERSE REACTIONS

See WARNINGS and Boxed Warning regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia.

The most commonly reported adverse reaction to the Climara® system in clinical trials was skin irritation at the application site. In two well-controlled clinical studies, the overall rate of discontinuation due to skin irritation at the application site was 6.8%: 7.9% for the 12.5 cm^2 system and 5.3% for the 25.0 cm^2 system compared with 11.5% for the placebo system. Patients with known skin irritation to the patch were excluded from participation in the studies. In a 3-week comparative skin irritation study with the Estraderm® system, in 95 subjects, no statistically significant differences in irritation were observed. Some degree of irritation at the end of week three was seen in 25% of Estraderm® and 31% of Climara® subjects. Clinically significant irritation (mild erythema associated with symptoms or moderate to severe erythema) was evident at the end of week three in 11% of Estraderm® and 9% of Climara® subjects. The following additional adverse reactions have been reported with estrogen therapy:

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.

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

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

6. **Central Nervous System.**
Headache, migraine, dizziness. Mental depression. Chorea.

7. **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

The adhesive side of the Climara® system should be placed on a clean, dry area of the lower abdomen or the upper quadrant of the buttock. *The Climara® system should not be applied to the breasts.* The sites of application must be rotated, with an interval of at least 1week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub and remove the system. Application to areas where sitting would dislodge the system should also be avoided. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the fingers for about 10 seconds, making sure there is good contact, especially around the edges. If the system lifts, apply pressure to maintain adhesion. In the event that a system should fall off, a new system should be applied for the remainder of the 7-day dosing interval. Only one system should be worn at any one time during the 7-day dosing interval. Swimming, bathing, or using a sauna while using the Climara® system has not been studied, and these activities may decrease the adhesion of the system and the delivery of estradiol.

Initiation of Therapy

Four (6.5, 12.5, 18.75 and 25.0 cm^2) Climara® systems are available.

For the treatment of vasomotor symptoms, treatment is usually initiated with the 12.5 cm^2 (0.05 mg/day) Climara® system applied to the skin once-weekly. The dose should be adjusted as necessary to control symptoms. Clinical responses (relief of symptoms) at the lowest effective dose should be the guide for establishing administration of the Climara® system, especially in women with an intact uterus. 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 the Climara® system can be initiated at once.

In women who are currently taking oral estrogen, treatment with the Climara® system can be initiated 1 week after withdrawal of oral therapy or sooner if symptoms reappear in less than 1 week.

For the prevention of postmenopausal osteoporosis, the minimum dose that has been shown to be effective is the 6.5 cm^2 (0.025 mg/day) Climara® system. Response to therapy can be assessed by biochemical markers and measurement of bone mineral density.

HOW SUPPLIED

Climara® (estradiol transdermal system), 0.025 mg/day - each 6.5 cm^2 system contains 2.04 mg of estradiol USP NDC 50419- 450-04
Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Climara® (estradiol transdermal system), 0.05 mg/day - each 12.5 cm^2 system contains 3.9 mg of estradiol USP NDC 50419-451-04
Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Climara® (estradiol transdermal system), 0.075 mg/day - each 18.75 cm^2 system contains 5.85 mg of estradiol USP NDC 50419-453-04
Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Climara® (estradiol transdermal system), 0.1 mg/day - each 25.0 cm^2 system contains 7.8 mg of estradiol USP NDC 50419-452-04
Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Do not store above 86° F (30° C). Do not store unpouched. Apply immediately upon removal from the protective pouch.

Rx only

Manufactured for Berlex Laboratories, Wayne, NJ 07470
Manufactured by 3M Pharmaceuticals, St. Paul, MN 55144

Berlex code number March 1999

MAR 5 1999 APPROVED

(3M #619700)

Climara
estradiol transdermal system
Continuous Delivery for
Once-Weekly Application

6064203

FPO

6064203

Climara
estradiol transdermal system
Continuous Delivery for
Once-Weekly Application

INFORMATION FOR THE PATIENT

INTRODUCTION

The Climara® system that your doctor has prescribed for you releases small amounts of estradiol through the skin in a continuous way. Estradiol is the same hormone that your ovaries produce abundantly before menopause. The dose of estradiol you require will depend upon your individual response. The dose is adjusted by the size of the Climara® system used; the systems are available in four sizes.

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

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 use estrogens, check with your doctor 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.

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.

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.

INFORMATION ABOUT CLIMARA®

How The Climara® System Works

The Climara® system contains 17β-estradiol. When applied to the skin as directed below, the Climara® system releases 17β-estradiol, which flows through the skin into the bloodstream.

How and Where to Apply the Climara® System

Each Climara® system is individually sealed in a protective pouch. To open the pouch, hold it vertically with the Climara® name facing you. Tear left to right using the top tear notch. Tear from bottom to top using the side tear notch. Pull the pouch open. The Climara® patch is the transparent plastic film attached to the clear thicker plastic backing. There is a silver-foil sticker securely attached to the inside of the pouch. This contains a moisture protectant (desiccant). Do not remove it. Carefully remove the Climara® patch. You'll notice that the patch is attached to a thicker, hard-plastic backing and that the patch itself is oval and transparent.

Apply the adhesive side of the Climara® system to a clean, dry area of the lower abdomen or the upper quadrant of the buttock. *Do not apply the Climara® system to your breasts.* The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub and remove the system. Application to areas where sitting would dislodge the system should also be avoided. Apply the system immediately after opening the pouch and removing the protective liner. Press the system firmly in place with the fingers for about 10 seconds, making sure there is good contact, especially around the edges.

The Climara® system should be worn continuously for one week. You may wish to experiment with different locations when applying a new system, to find ones that are most comfortable for you and where clothing will not rub on the system.

When to Apply the Climara® System

The Climara® system should be changed once weekly.

When changing the system, remove the used Climara® system and discard it. Any adhesive that might remain on your skin can be easily rubbed off. Then place the new Climara® system on a different skin site. (The same skin site should not be used again for at least 1 week after removal of the system.)

Contact with water when you are bathing, swimming, or showering will not affect the system. In the unlikely event that a system should fall off, a new system should be applied for the remainder of the 7-day dosing interval.

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.)

- **To reduce moderate or 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".

  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. Most women have only mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.

- **To treat vulval 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.**
- **To treat certain types of abnormal vaginal 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.**
- **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.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

- **During pregnancy (see Boxed Warning).**

  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 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.

- **If you have had cancer.**

  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.**

  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 Dangers of Estrogens, below).

- **When they do not work.**

  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.**

  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 Dangers 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.

DANGERS OF ESTROGENS

- **Cancer of the uterus.**

  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 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 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 danger 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.

- **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. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

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.
- 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.

REDUCING RISK OF ESTROGEN USE

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

- **See your doctor regularly.**

  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.

- **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.**

  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)

  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)

  Yellowing of the skin or eyes (possible liver problem)

  Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

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 doctors 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 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.

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

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.

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 book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

Do not store above 86° F(30° C). Do not store unpouched. Apply immediately upon removal from the protective pouch.

CAUTION: Federal law prohibits dispensing without prescription.

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Manufactured by 3M Pharmaceuticals, St. Paul, MN 55144

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APPEARS THIS WAY
ON ORIGINAL