CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-375/S-009

FINAL PRINTED LABELING

APPROVED

MAR 3

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.

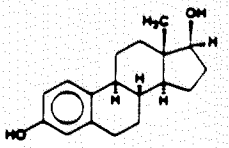
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY
Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that 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. Three (12.5, 18.75 and 25.0 cm^2) systems are available to provide nominal *in vivo* delivery of 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 12.5, 18.75 or 25.0 sq cm, and contains 3.9 or 7.8 mg of estradiol USP respectively. The composition of the systems per unit area is identical. 5.8

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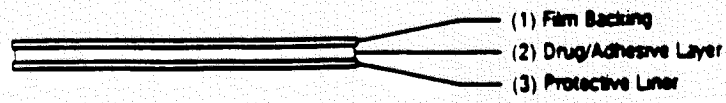
The Climara® system comprises two layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film, and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymer-coated polyester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



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

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone — especially in its sulfate ester form — is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

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

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms, which are continually interconverted, especially between estrone and estradiol and between esterified and unesterified forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active

estrogenic species. A certain proportion of the estrogen is excreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. In contrast, the skin metabolizes estradiol only to a small extent. Therefore, transdermal administration produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates, and requires smaller total doses than does oral therapy. Because estradiol has a short half-life, transdermal administration of estradiol allows a rapid decline in blood levels after the Climara® system is removed.

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 173 healthy postmenopausal women in five studies. In four of the studies Climara® system was applied to the abdomen and in a fifth 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 sq cm Climara® systems versus the 20 and 10 sq cm Estraderm® systems are shown in Figures 1 and 2, 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 was 3 to 4 times lower with the Climara® system.

Figure 1
Observed Mean (± S.E.) Estradiol Serum Concentrations for a One Week Application of the Climara® system (25 sq cm) and Consecutive Three Day and Four Day Application of the Estraderm® System (20 sq cm) in 24 postmenopausal women

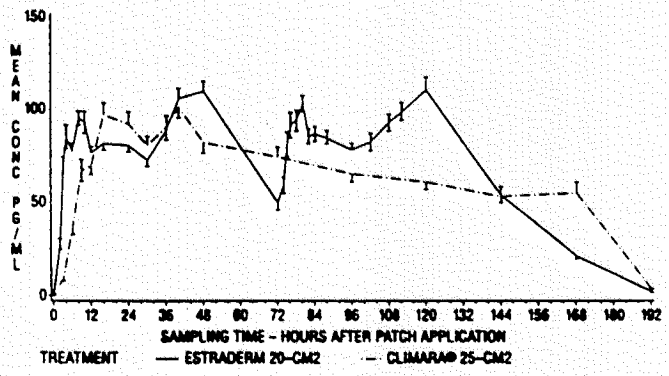
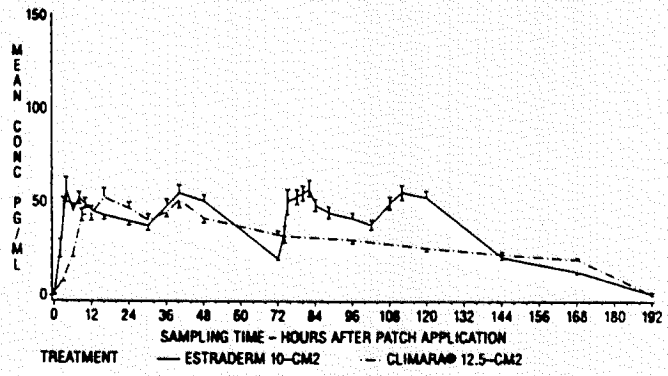


Figure 2
Observed Mean (± S.E.) Estradiol Serum Concentrations for a One Week Application of the Climara® system (12.5 sq cm) and Consecutive Three Day and Four Day Application of the Estraderm® System (10 sq cm) in 24 postmenopausal women



Dose proportionality was demonstrated for the Climara® system in a 1 week study conducted in 54 postmenopausal women. The mean steady state levels (Cavg) of the estradiol during the application of Climara 25 sq cm and 12.5 sq cm 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 3. Cmax and Cavg values were, respectively, 25% and 17% higher with the buttock application than

with the abdomen application. Despite these pharmacokinetics differences, it is expected that Climara® applied to either of the two sites will have similar clinical effects.

Figure 3.
Observed Mean (± S.E.) Estradiol Serum Concentrations for a One Week Application of the Climara® system (25 sq cm) to the abdomen and buttocks of 38 postmenopausal women

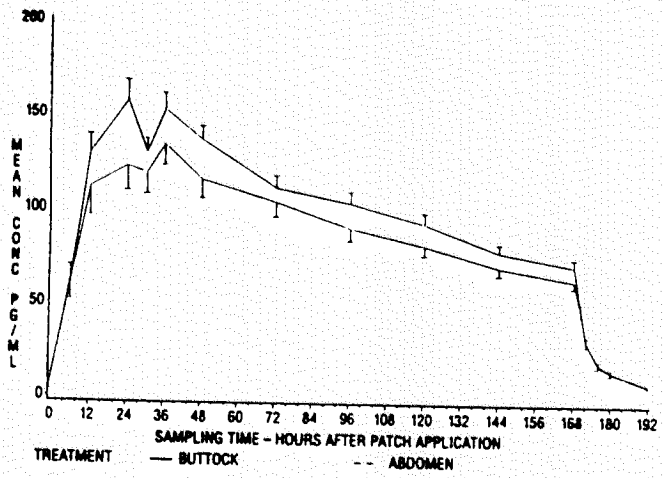


Table 1 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of Climara®.

Table 1
Pharmacokinetic Summary
(Mean Estradiol Values)

Climara® Delivery Rate	Surface Area (sq cm)	Application Site	No. of Subjects	Dosing	Cmax (pg/mL)	Cmin (pg/mL)	Cavg (pg/mL)
0.05	12.5	Abdomen	78	Single	75	28	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: Estradiol circulates in blood bound to sex hormone binding globulin (SHBG) and albumin. Following transdermal administration of estradiol about 98% of estradiol and about 97% of estrone are reported to be bound to plasma proteins in post menopausal women. The protein binding of estradiol and estrone as well as the concentration of SHBG were unchanged following three months of transdermal treatment. In postmenopausal women with end stage renal disease, the plasma protein binding of estradiol is reported to be decreased.

Metabolism: 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. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary excretion 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. The hepatic first pass effect is avoided with transdermal estrogens, but the clinical significance of this has not been fully established.

Excretion: Estrodiol, estrone, and estriol are excreted in the urine mainly as glucuronide and sulfate conjugates and less than 1% as unconjugated sterioids. 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 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.

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. Other studies have not shown this relationship.

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 which 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 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 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. 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 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 which 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 sq cm system and 5.3% for the 25.0 sq cm system compared with 11.5% for the placebo system. 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 quandrant 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 1 week 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.

Initiation of Therapy

Three (12.5, 18.75 and 25.0 cm^2 Climara® systems are available. Treatment is usually initiated with the 12.5 sq cm (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.

Therapeutic Regimen

Therapy with the Climara® system is usually administered on a cyclic schedule (e.g., 3 weeks of therapy followed by 1 week without) especially in women with an intact uterus, who are not using concomitant progestin therapy.

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HOW SUPPLIED

Climara® (estradiol transdermal system), 0.05 mg/day - each 12.5 sq cm 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-XXX-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 sq cm 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.

CAUTION: Federal law prohibits dispensing without prescription.

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

6064303.doc Sept 1997

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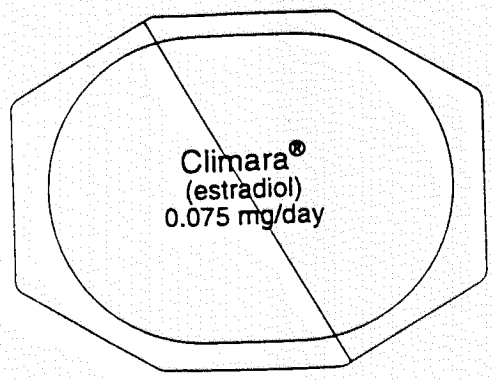
CLIMARA® estradiol transdermal system
0.075mg/day
Patch Labeling



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MAR 23 2000

CLIMARA® estradiol transdermal system
0.075mg/day
Pouch Labeling

NDC 50419-XXX-04

CLIMARA®
estradiol transdermal system
0.075 mg/day

Contents:
One 18.75cm^2 system containing 5.85mg estradiol USP to provide 0.075mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing. release liner

Caution: Federal law prohibits dispensing without prescription.

Do not store unpouched. Do not store above 86°F (30°C).

See patient instructions for application. Apply immediately upon removal from pouch. Each Climara estradiol transdermal system is intended to be worn for 7 days.

Keep this and all drugs out of the reach of children.

Mfd for:
Berlex Laboratories, Wayne, NJ 07470

Mfd by:
3M Pharmaceuticals, St. Paul, MN 55144-1000

LOT
EXP

APPROVED

MAR 3

CLIMARA® estradiol transdermal system
0.075mg/day
Carton Labeling

NDC 50419-XXX-04 4 systems

CLIMARA®
estradiol transdermal system
0.075 mg/day

Contents:
One 18.75cm^2 system containing 5.85mg estradiol USP to provide 0.075mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

For transdermal use only

Keep this and all drugs out of the reach of children.

Caution: Federal law prohibits dispensing without prescription.

Do not store unpouched. Do not store above 86°F (30°C).

Dosage and Administration: See package insert. Apply immediately upon removal from pouch.

Each Climara estradiol transdermal system is intended to be worn for 7 days.

AFFIX R_x LABEL HERE

Mfd for:
Berlex Laboratories, Wayne, NJ 07470

Mfd by:
3M Pharmaceuticals, St. Paul, MN 55144-1000

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