Rx Only

PRESCRIBING INFORMATION **Climara® estradiol transdermal system**

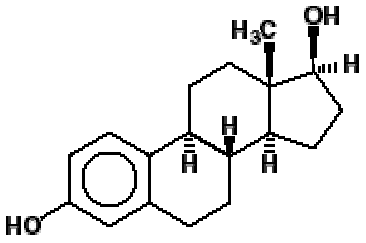
1. ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen doses.

2. 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.

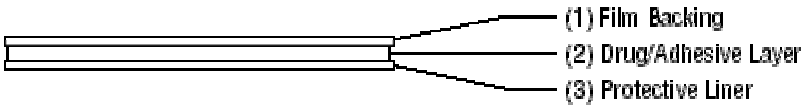
DESCRIPTION

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 2.0, 3.8, 5.7 or 7.6 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:



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.

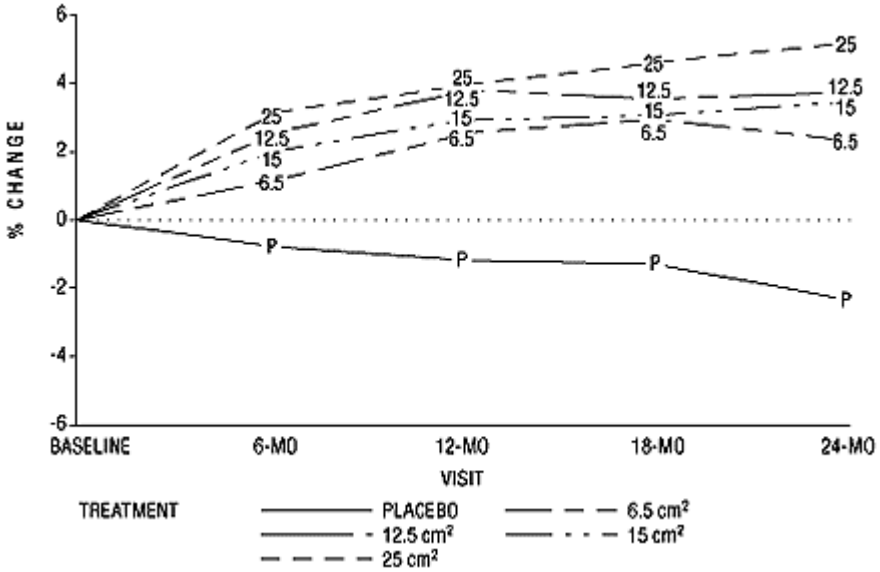
Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially 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.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

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

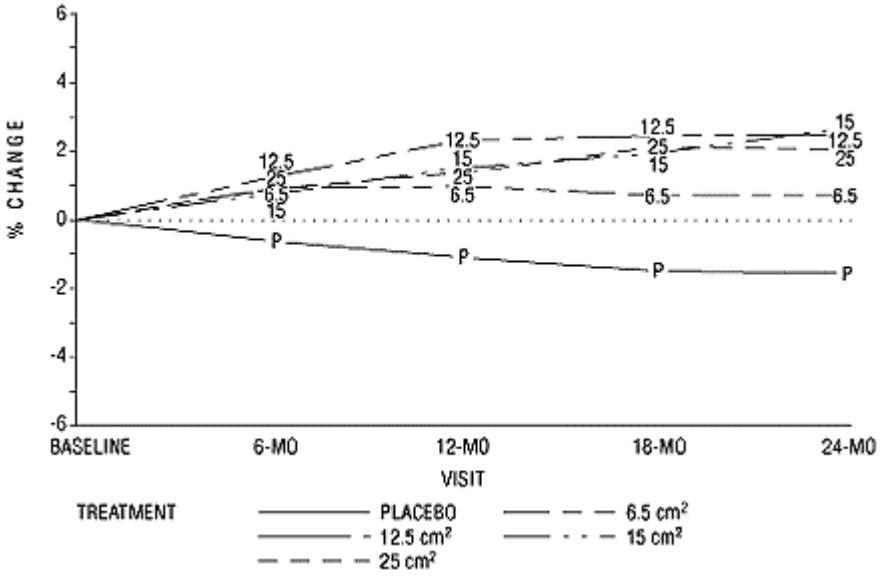
A two-year clinical trial enrolled a total of 175 healthy, hysterectomized, postmenopausal, non-osteoporotic (i.e., lumbar spine bone mineral density > 0.9 gm/cm^2) women at 10 study centers in the United States. 129 subjects were allocated to receive active treatment with 4 different doses of 17 β-estradiol 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**



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 Percent 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).

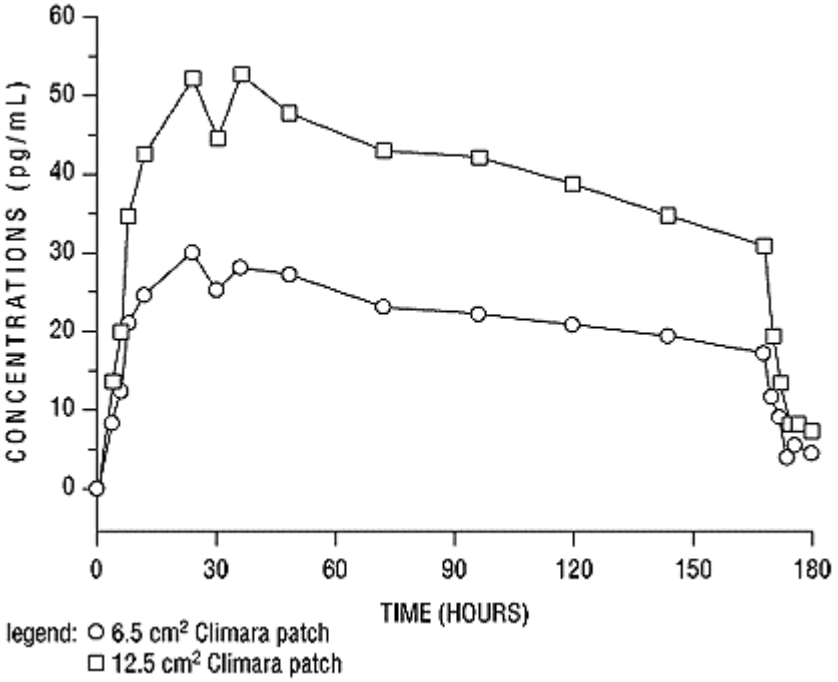
PHARMACOKINETICS

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 a 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.

In a 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 two sizes are shown in Figure 3.

Figure 3
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.



Dose proportionality was demonstrated for the Climara® 6.5 cm^2 transdermal system as compared to the Climara® 12.5 cm^2 transdermal system in a 2-week crossover study with a 1-week washout period between the two transdermal systems in 24 postmenopausal women.

Dose proportionality was also demonstrated for the Climara® system (12.5 cm^2 and 25 cm^2) 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 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 cm^2 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 cm^2 system for one week on the abdomen and buttocks. The estradiol serum concentration profiles are shown in Figure 4. Cmax and Cavg values were, respectively, 25% and 17% higher with the buttock application than with the abdomen application.

Figure 4.
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.

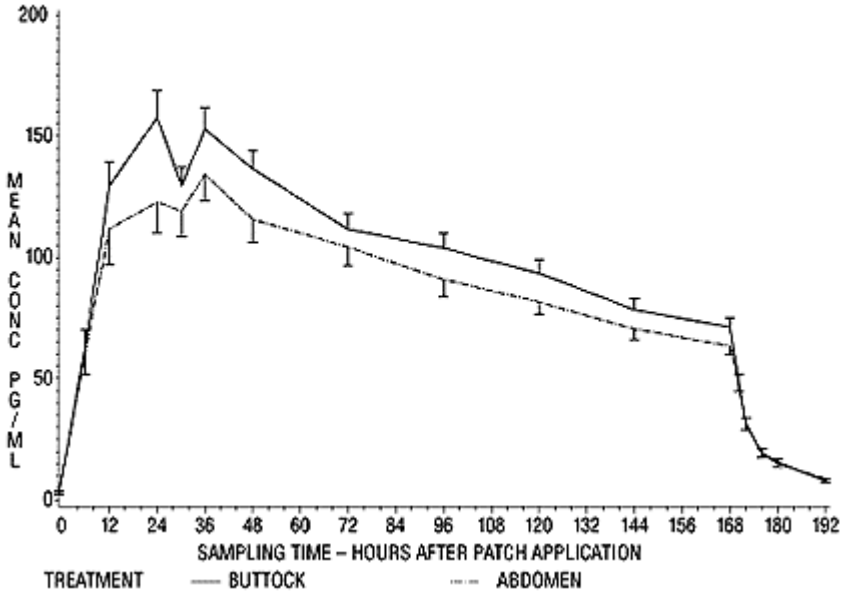


Table 1 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of Climara®.

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:

Geriatric: There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing Climara® to determine whether those over 65 years of age differ from younger subjects in their response to Climara®.

Pediatric: No pharmacokinetic study for Climara® has been conducted in a pediatric population.

Gender: Climara® is indicated for use in women only.

Race: No studies were done to determine the effect of race on the pharmacokinetics of Climara®.

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.

Drug Interactions: No drug interaction studies have been conducted.

Adhesion

An open-label study of adhesion potentials of placebo transdermal systems that correspond to the 6.5 cm^2 and 12.5 cm^2 sizes of Climara® was conducted in 112 healthy women of 45-75 years of age. Each woman applied both transdermal systems weekly, on the upper outer abdomen, for three consecutive weeks. It should be noted that lower abdomen and upper quadrant of the buttock are the approved sites of application for Climara®.

The adhesion assessment was done visually on Days 2, 4, 5, 6, 7 of each week of transdermal system wear. A total of 1654 adhesion observations were conducted for 333 transdermal systems of each size.

Of these observations, approximately 90% showed essentially no lift for both the 6.5 cm^2 and 12.5 cm^2 transdermal systems. Of the total number of transdermal systems applied, approximately 5% showed complete detachment for each size.

Adhesion potentials of the 18.75 cm^2 and 25.0 cm^2 sizes of transdermal systems (0.075 mg/day and 0.1 mg/day) have not been studied.

Clinical Studies

Climara® is effective in reducing moderate to severe vasomotor symptoms in postmenopausal women.

A total of 214 patients were enrolled in a study, to determine the efficacy of Climara® 0.05 mg/day and 0.1 mg/day compared to placebo and an active comparator. Women took drug in a cyclical fashion (three weeks on and one week off).

A study of 214 women 25 to 74 years old met the qualification criteria and were randomly assigned to one of the three treatment groups: 72 to the 0.05 mg estradiol patch, 70 to the 0.1 mg estradiol patch, and 72 to placebo. Potential subjects were postmenopausal women in good general health who experienced vasomotor symptoms. Natural menopause patients had not menstruated for at least 12 months and surgical menopause patients had undergone bilateral oophorectomy at least four weeks before evaluation for study entry. In order to enter the 11-week treatment phase of the study, potential subjects must have experienced a minimum of five moderate to severe hot flushes per week, or a minimum of 15 hot flushes of any severity per week, for two consecutive weeks. Women wore the patches in a cyclical fashion (three weeks on and one week off).

During treatment, all subjects used diaries to record the number and severity of hot flushes. Subjects were monitored by clinic visits at the end of Weeks 1, 3, 7, and 11 and by telephone at the end of Weeks 4, 5, 8, and 9.

Adequate data for the analysis of efficacy was available from 191 subjects. The results are presented as the mean ± SD number of flushes in each of the three treatment weeks of each 4-week cycle. In the 0.05 mg estradiol group, the mean weekly hot flush rate across all treatment cycles decreased from 46 ± 6.5 at baseline to 20 ± 3.0 (-67.0%). The 0.1 mg estradiol group had a decline in the mean weekly hot flush rate from 52 ± 4.4 at baseline to 16 ± 2.4 (-72.0%). In the placebo group, the mean weekly hot flush rate declined from 53 ± 4.5 at baseline to 46 ± 6.5 (-18.1%). Compared with placebo, the 0.05 mg and 0.1 mg estradiol groups showed a statistically significantly larger mean decrease in hot flushes across all treatment cycles ($P < 0.05$). When the response to treatment was analyzed for each of the three cycles of therapy, similar statistically significant differences were observed between both estradiol treatment groups and the placebo group during all treatment cycles.

In a double-blind, placebo-controlled, randomized study of 187 women receiving Climara® 0.025 mg/day or placebo continuously for up to three 28-day cycles, the Climara® 0.025 mg/day dosage was shown to be statistically better than placebo at Weeks 4 and 12 for relief of both the frequency (see Table 3) and severity of moderate-to-severe vasomotor symptoms.

Table 3
Mean Change from Baseline in the Number of Moderate-to-Severe Vasomotor Symptoms (ITT)

Treatment Group	Statistics	Week 4	Week 8	Week 12
E_2 TDS	N	82	84	68
	Mean	-6.45	-7.69	-7.56
	SD	4.65	4.76	4.64
Placebo	N	83	71	65
	Mean	-5.11	-5.98	-5.98
	SD	7.43	8.63	9.69
	p-Value	<0.002		<0.003

A second active-control trial of 193 randomized subjects was supportive of the placebo-controlled trial.

INDICATIONS AND USAGE

Climara® is indicated in the:

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

2. Treatment of vulvar and vaginal atrophy.

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

4. Prevention of postmenopausal osteoporosis (loss of bone mass). The mainstays of prevention of postmenopausal osteoporosis are weight bearing exercise, an adequate calcium and vitamin D intake, and when indicated, estrogen. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500mg/day of elemental calcium to remain in neutral calcium balance. The average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake.

Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. 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.

Early menopause is one of the strongest predictors for the development of osteoporosis in all women. Other factors associated with osteoporosis include genetic factors, lifestyle and nutrition.

CONTRAINDICATIONS

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

1. Known or suspected pregnancy (see **PRECAUTIONS**). 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.

6. Climara® should not be used in patients hypersensitive to its ingredients.

WARNINGS

1. **Induction of malignant neoplasms.**

a. Endometrial cancer.

The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use-, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

b. Breast Cancer.

While some epidemiologic studies suggest a very modest increase in breast cancer risk for estrogen alone users versus non-users, other studies have not shown any increased risk. The addition of progestin to estrogen may increase the risk for breast cancer over that noted in non-hormone users more significantly (by about 24-40%), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials.

Women without a uterus who require hormone replacement should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. Women with a uterus who are candidates for short-term combination estrogen/progestin therapy (for relief of vasomotor symptoms) are not felt to be at a substantially increased risk for breast cancer. Women with a uterus who are candidates for long-

term use of estrogen/progestin therapy should be advised of potential benefits and risks (including the potential for an increased risk of breast cancer). All women should receive yearly breast exams by a health-care provider and perform monthly self-breast examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.

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

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

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

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.

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

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

There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include: (a) adverse effects on lipoprotein metabolism (e.g., lowering HDL and raising LDL) and (b) impairment of glucose tolerance. The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects.

2. **Cardiovascular risk**. The effects of estrogen replacement on the risk of cardiovascular disease have not been adequately studied. However, data from the Heart and Estrogen/Progestin Replacement Study (HERS), a controlled clinical trial of secondary prevention of 2,763 postmenopausal women with documented heart disease, demonstrated no benefit. During an average follow-up of 4.1 years, treatment with oral conjugated estrogen plus medroxyprogesterone acetate did not reduce the overall rate of coronary heart disease (CHD) events in post-menopausal women with established coronary disease. There were more CHD events in the hormone treated group than in the placebo group in year 1, but fewer events in years 3 through 5.

3**. Elevated blood pressure**. In a small number of case reports, substantial increases in blood pressure during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.

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

5. **Impaired liver function** Estrogens may be poorly metabolized in patients with impaired liver function.

6. **Hypothyroidism.** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy, however, may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range.

7. **Fluid retention.** Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine and cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

8. **Exacerbation of endometriosis**. Endometriosis may be exacerbated with administration of estrogen therapy.

9. **Hypocalcemia.** Estrogens should be used with caution in individuals with severe hypocalcemia.

B. **Patient Information**. See text of Patient Information 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**. 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**. Climara® should not be used during pregnancy. See **CONTRAINDICATIONS**.

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

H. **Pediatric Use**. Estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding. In boys, estrogen treatment may modify the normal pubertal process and induce gynecomastia. (See **INDICATIONS** and **DOSAGE AND ADMINISTRATION** section.)

I. **Geriatric Use**. There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing Climara® to determine whether those over 65 years of age differ from younger subjects in their response to Climara®.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed

in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

See **WARNINGS** regarding induction of neoplasia, increased incidence of gallbladder disease, cardiovascular disease, and hypercalcemia; see **PRECAUTIONS** regarding cardiovascular risk and elevated blood pressure.

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. The following additional adverse reactions have been reported with estrogen therapy:

Summary of Most Frequently Reported Adverse Experiences/Medical Events (≥5%) by Treatment Groups

	Climara®			
AE per Body System	**0.025 mg/day (N=219)**	**0.05 mg/day (N=201)**	**0.1 mg/day (N=194)**	**Placebo (N=72)**
Body as a Whole	21%	39%	37%	29%
Headache	5%	18%	13%	10%
Pain	1%	8%	11%	7%
Back Pain	4%	8%	9%	6%
Edema	0.5%	13%	10%	6%
Gastro-Intestinal	9%	21%	29%	18%
Abdominal Pain	0.0%	11%	16%	8%
Nausea	1%	5%	6%	3%
Flatulence	1%	3%	7%	1%
Musculo-Skeletal	7%	9%	11%	4%
Arthralgia	1%	5%	5%	3%
Psychiatric	13%	10%	11%	1%
Depression	1%	5%	8%	0%
Reproductive	12%	18%	41%	11%
Breast Pain	5%	8%	29%	4%
Leukorrhea	1%	6%	7%	1%
Respiratory	15%	26%	29%	14%
URTI	6%	17%	17%	8%
Pharyngitis	0.5%	3%	7%	3%
Sinusitis	4%	4%	5%	3%
Rhinitis	2%	4%	6%	1%
Skin and Appendages	19%	12%	12%	15%
Pruritus	0.5%	6%	3%	6%

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 one 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. 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 should be initiated with the 6.5 cm^2 (0.025 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 2.0 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 3.8 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 5.7 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 7.6 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.

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

CLIMARA®

(estradiol transdermal system)

Rx only

PATIENT INFORMATION

The Climara® patch that your healthcare provider has prescribed for you releases small amounts of an estrogen hormone through the skin.

This leaflet describes the risks and benefits of treatment with Climara®. Climara® is not for everyone. Talk to your health care provider if you have any questions or concerns about this medicine.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT CLIMARA® ?

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS
If you use any drug that contains estrogen, it is important to visit your doctor of health care provider regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor or health care provider should evaluate any unusual vaginal bleeding to find out the cause. Women who do not have a uterus have no risk of endometrial cancer.

What is Climara®?

Climara® (pronounced Cly-MARE-a) is a patch that contains an estrogen hormone called 17β-estradiol. When applied to the skin as directed below, the Climara® patch releases estrogen through the skin into the bloodstream.

CLIMARA® IS APPROVED FOR USE IN THE FOLLOWING WAYS:

- **To reduce moderate or severe menopausal symptoms.**
  Estrogens are hormones made by a woman's ovaries. When a women is between the ages of 45 and 55, the ovaries normally stop making estrogens. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). 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"). In some women the symptoms are mild and in others they can be severe. 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 itching, burning and dryness in and around the vagina associated with menopause.**

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

- **To help reduce your chances of getting osteoporosis (thin weak bones).**
  Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. Climara® may be used as part of a program of weight-bearing exercise like walking and running and calcium supplements to reduce your chances of getting 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. Women who are more likely to develop osteoporosis often have one or more of the following characteristics: white or Asian race, slim body frame, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have menopause at an earlier age either naturally or because their ovaries were removed during an operation, are more likely to develop osteoporosis than women whose menopause happens later in life.

WHO SHOULD NOT USE CLIMARA®

Climara® should not be used in the following situations:

- **During pregnancy.**
  If you think you may be pregnant, do not use Climara® . Using Climara® while you are pregnant may harm your unborn child. Do not use Climara® to prevent miscarriage.

- **If you have unusual vaginal bleeding that has not been checked by your healthcare provider.**
  Unusual vaginal bleeding can be a warning sign of serious conditions including cancer of the uterus, especially if it happens after menopause. Your healthcare provider must find out the cause of the bleeding so that he or she can recommend the proper treatment.

- **If you have had cancer.**
  Estrogens increase the risk of certain types of cancer, including cancer of the breast or uterus. If you have had cancer, talk to your healthcare provider about the use of Climara®.

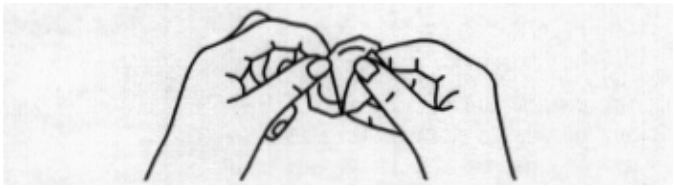
- **If you have any circulation problems.**
  Talk with your doctor about your condition. Do not take Climara® if you have blood clots or have had them in the past.

- **After childbirth or when breastfeedlng a baby.**
  Do not use Climara® to stop the breasts from filling with milk after a baby is born.

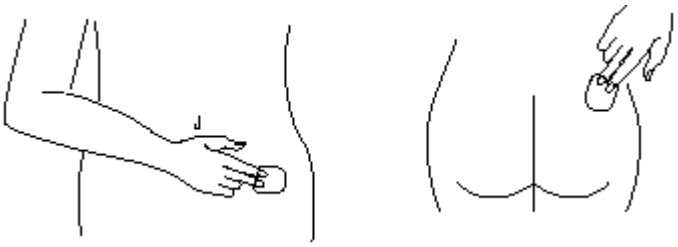
- **If you are allergic to Climara® or any of the ingredients in it.**

How and Where to Apply the Climara® Patch.

Each Climara® patch is individually sealed in a protective pouch. To open the pouch, hold it with the Climara® name facing you. Tear off the top of the pouch using the top tear notch. Tear off the side of the pouch using the side tear notch. Pull the pouch open. The Climara® patch is the see-through plastic film attached to the clear thicker plastic backing. There is a silver foil-sticker attached to the inside of the pouch. **Do not remove it from the pouch.** The sticker contains a moisture protectant (desiccant). **Lift out the Climara® patch.** Notice that the patch is attached to a thicker, hard-plastic backing and that the patch itself is oval and see-through.



Apply the sticky side of the Climara® patch to a clean, dry area of the lower stomach below your belly button or the top of the buttocks (see diagram below). *Do not apply the Climara® patch to your breasts.* The sites of application on the lower stomach and buttocks must be rotated, allowing at least 1 week between applications to the same site. The site selected should not be oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub and remove the patch. Also, do not put the patch on areas where sitting would rub it off or loosen it. Apply the patch right after opening the pouch and removing the protective liner. Press the patch firmly in place with your fingers for about 10 seconds. Make sure that it sticks all over, especially around the edges.



The Climara patch should be worn continuously for one week. You may wish to try different sites when putting on a new patch, to find ones that are most comfortable for you and where clothing will not rub on the patch or loosen it.

When to Apply the Climara® System?

The Climara® patch should be changed once a week.
When changing the patch, peel off the used Climara® patch and throw it away. Any sticky material that might stay on your skin can be easily rubbed off. Then place a new Climara® patch on a different skin site. (Do not use the same skin site over again for at least one week.)

Tub bathing or swimming could loosen the patch. In the event that a patch should fall off, a new patch should be put on for the rest of the 7-day period.

WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS OF CLIMARA®?

Common side effects include;

- 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.

Less common but serious effects include:

- Cancer of the uterus.
- Cancer of the breast.
- Gallbladder disease.
- Abnormal blood clotting**.**

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

- 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). Check your breasts every month. Ask your doctor or health professional to show you how to examine your breasts.
- Yellowing of the skin or whites of the eyes (possible liver problem)
- Pain, swelling, or tenderness in the abdomen (stomach area; possible gallbladder problem).

What can I do to lower my chances of getting a serious side effect with Climara®?
If you use Climara®, you can reduce your risks by doing these things:

- **See your health care provider regularly.**
  While you are using Climara®, it is important to visit your health care provider at least once a year for a check-up. If you develop vaginal bleeding while taking Climara®, 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.

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

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Climara® for condition for which it was not prescribed. Do not give Climara® to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Climara®. If you would like more information, talk with your healthcare provider. You can ask for information about Climara® that is written for health professionals.

Manufactured for:
BERLEX Laboratories, Wayne, NJ 07470

Manufactured by 3M Pharmaceuticals, St. Paul, MN 55144
Berlex Component Code # March. 2001