Rx Only

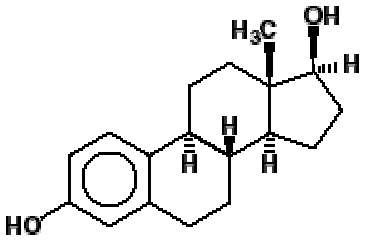
PRESCRIBING INFORMATION **Climara® estradiol transdermal system**

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.

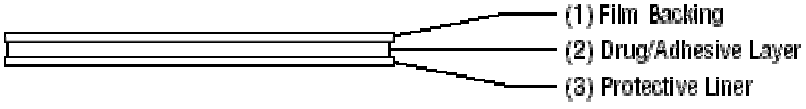
DESCRIPTION

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.

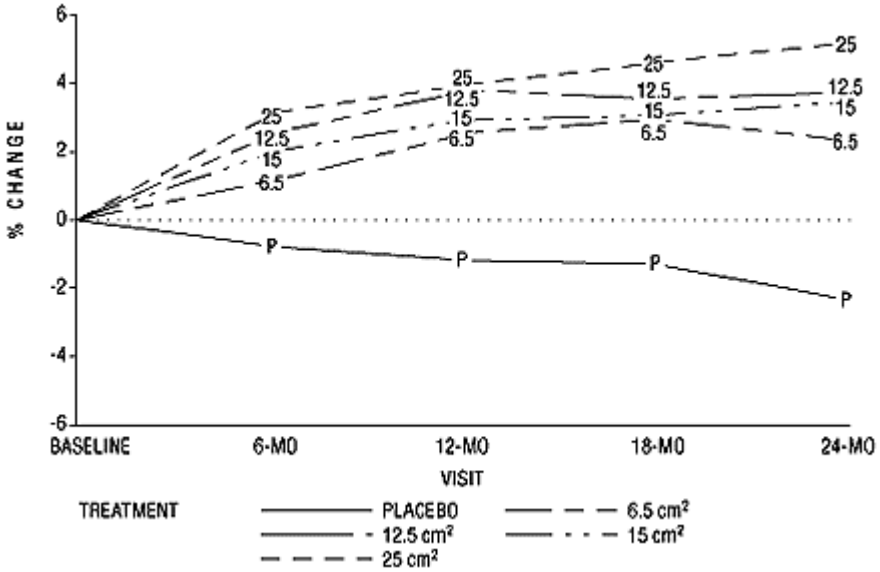
Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially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

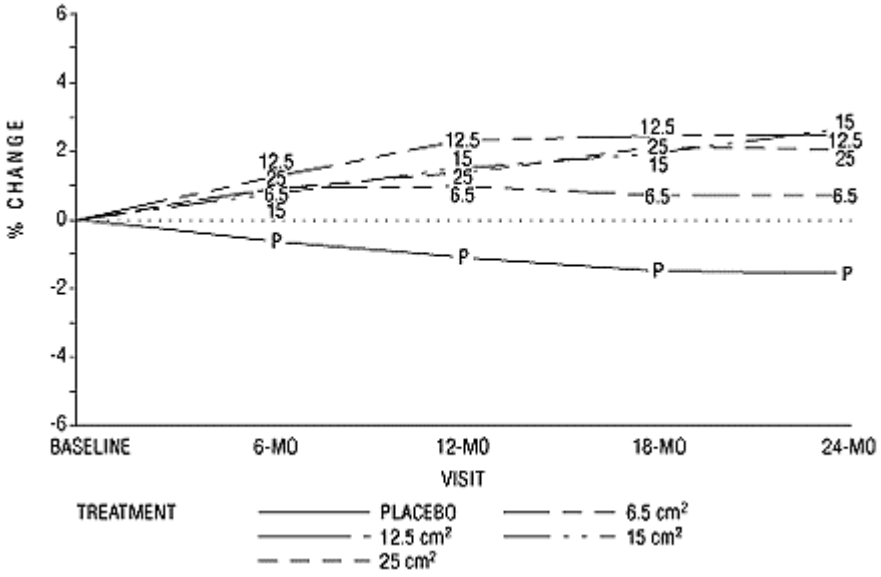
A two-year clinical trial enrolled a total of 175 healthy, hysterectomized, postmenopausal, non-osteoporotic (i.e., lumbar spine bone mineral density > 0.9 gm/cm^2) women at 10 study centers in the United States. 129 subjects were allocated to receive active treatment with 4 different doses of 17 β-estradiol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

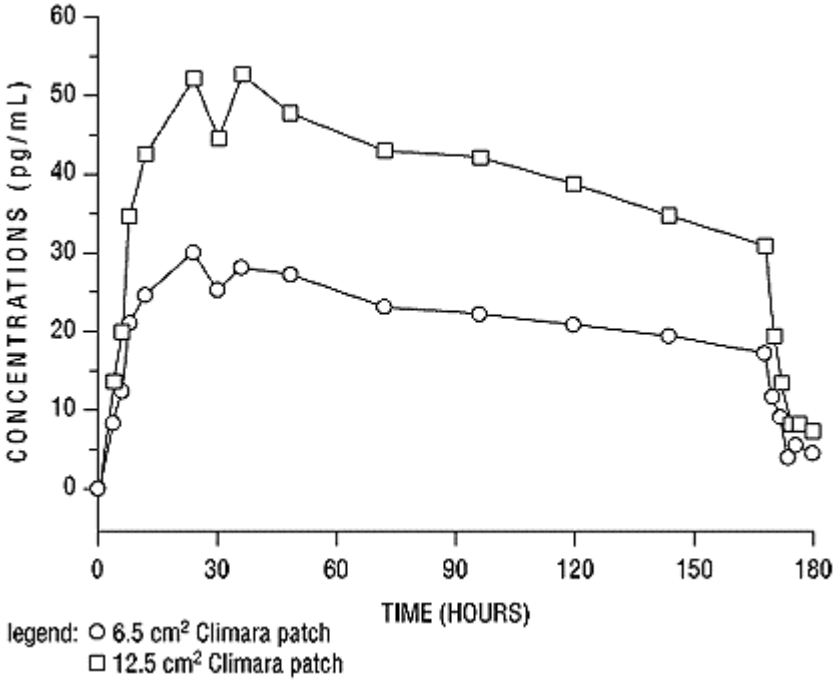
PHARMACOKINETICS

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 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 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.

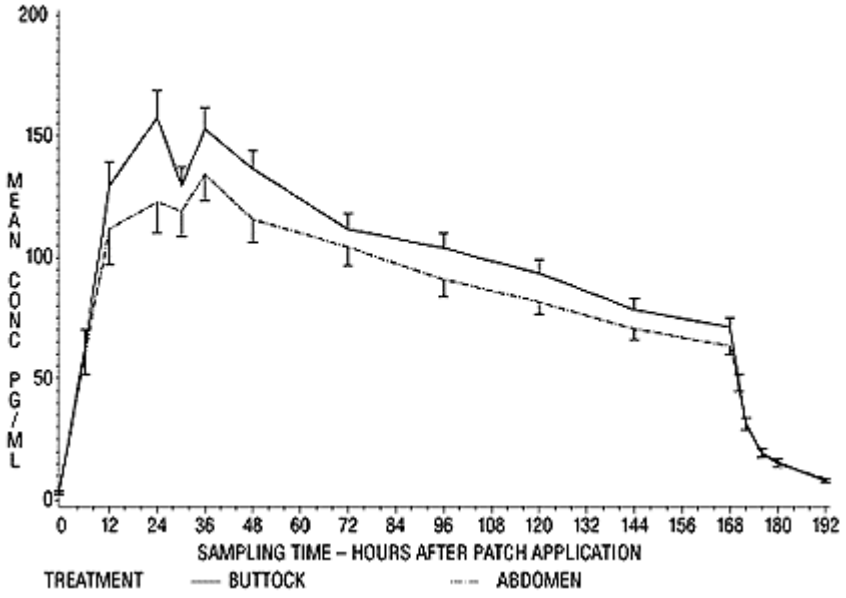


Table 1 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of Climara®.

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 4 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 2 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 3 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.

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=32)**	**0.05 mg/day (N=201)**	**0.1 mg/day (N=194)**	**Placebo (N=72)**
Body as a Whole	43.8%	39%	37%	29%
Headache	12.5%	18%	13%	10%
Pain	0.0%	8%	11%	7%
Back Pain	12.5%	8%	9%	6%
Edema	0.0%	13%	10%	6%
Gastro-Intestinal	12.5%	21%	29%	18%
Abdominal Pain	0.0%	11%	16%	8%
Vomiting	0.0%	3%	8%	6%
Nausea	0.0%	5%	6%	3%
Flatulence	0.0%	3%	7%	1%
Musculo-Skeletal	31.3%	9%	11%	4%
Arthralgia	6.3%	5%	5%	3%
Psychiatric	31.3%	10%	11%	1%
Depression	6.3%	5%	8%	0%
Respiratory	28.1%	26%	29%	14%
URTI	3.1%	17%	17%	8%
Pharyngitis	3.1%	3%	7%	3%
Sinusitis	15.6%	4%	5%	3%
Rhinitis	9.4%	4%	6%	1%
Skin and Appendages	43.8%	12%	12%	15%
Pruritus	0.0%	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 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. 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 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 2.0 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)

Continuous Delivery for
Once Weekly Application

Rx only

INFORMATION FOR THE PATIENT INTRODUCTION
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.

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.

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

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.

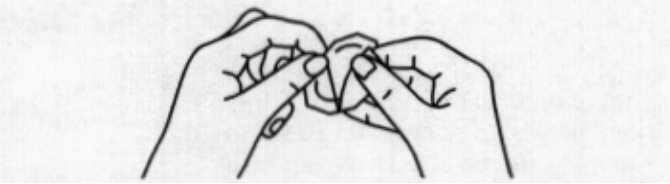
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed In the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing 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-estra-diol, 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 **RISKS 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 breastfeedlng a baby.**

  Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see RISKS **OF ESTROGENS, BELOW).** If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health care provider.

RISKS OF ESTROGENS

- **Cancer of the uterus.**

  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.**

  Studies examining the risk of breast cancer among women using estrogen alone and combined estrogen/progestin therapy have suggested that there may be a mildly increased risk of breast cancer in women taking the combined therapy.

  If you do not have your uterus, there is no need for combined estrogen/progestin therapy since estrogen alone therapy is sufficient and may pose less risk for breast cancer.

  If you do have your uterus, you should discuss the benefits and risks of combined estrogen/progestin therapy with your health care provider. Regular breast exams by a health professional and monthly self-exams are recommended for all women. Mammography may also be recommended depending on your age and risk factors.

- **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.

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