NOVARTIS

T2000-61/T2000-62
89009702

Estraderm®

estradiol transdermal system
Continuous delivery for twice-weekly application

Rx only

Prescribing Information

1. **ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.**

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. **ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.**

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possible testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

There is no indication for estrogen therapy during pregnancy. 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

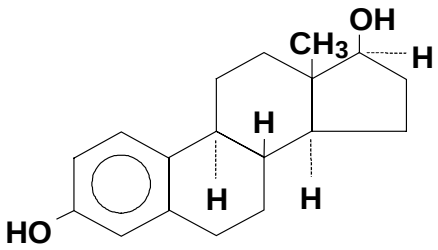
Estraderm, estradiol transdermal system, is designed to release estradiol through a rate-limiting membrane continuously upon application to intact skin.

Two systems are available to provide nominal in vivo delivery of 0.05 or 0.1 mg of estradiol per day via skin of average permeability (interindividual variation in skin permeability is approximately 20%). Each corresponding system having an active surface area

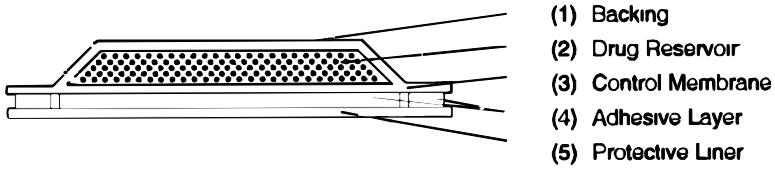
of 10 or 20 cm^2 contains 4 or 8 mg of estradiol USP and 0.3 or 0.6 mL of alcohol USP, respectively. The composition of the systems per unit area is identical.

Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5 (10)-triene-3,17ß-diol.

The structural formula is



The Estraderm system comprises four layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a transparent polyester film, (2) a drug reservoir of estradiol USP and alcohol USP gelled with hydroxypropyl cellulose, (3) an ethylene-vinyl acetate copolymer membrane, and (4) an adhesive formulation of light mineral oil and polyisobutylene. A protective liner (5) of siliconized polyethylene terephthalate film is attached to the adhesive surface and must be removed before the system can be used.



The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive. Alcohol is also released from the system during use.

CLINICAL PHARMACOLOGY

The Estraderm system releases estradiol, the major estrogenic hormone secreted by the human ovary. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor level.

Estraderm provides systemic estrogen replacement therapy. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and in the bone of women. Among numerous effects, estradiol is largely responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. By a direct action, it causes growth and development of the vagina, uterus, and fallopian tubes. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens contribute to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the

long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and to the pigmentation of the nipples and genitals.

Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy and affect the release of pituitary gonadotropins.

Loss of ovarian estradiol secretion after menopause can result in instability of thermoregulation, causing hot flushes associated with sleep disturbance and excessive sweating, and urogenital atrophy, causing dyspareunia and urinary incontinence. Estradiol replacement therapy alleviates many of these symptoms of estradiol deficiency in the menopausal woman.

Transdermal administration produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates and requires smaller total doses than does oral therapy. Because estradiol has a short half-life (~1 hour), transdermal administration of estradiol allows a rapid decline in blood levels after an Estraderm system is removed, e.g., in a cycling regimen.

In a study using transdermally administered estradiol, 0.1 mg daily, plasma levels increased by 66 pg/mL, resulting in an average plasma level of 73 pg/mL. There were no significant increases in the concentration of renin substrate or other hepatic proteins (sex hormone-binding globulin, thyroxine-binding globulin, and corticosteroid-binding globulin).

Pharmacokinetics

Administration of Estraderm produces mean serum concentrations of estradiol comparable to those produced by daily oral administration of estradiol at about 20 times the daily transdermal dose. In single-application studies in 14 postmenopausal women using Estraderm systems that provided 0.05 and 0.1 mg of exogenous estradiol per day, these systems produced increased blood levels within 4 hours and maintained respective mean serum estradiol concentrations of 32 and 67 pg/mL above baseline over the application period. At the same time, increases in estrone serum concentration averaged only 9 and 27 pg/mL above baseline, respectively. Serum concentrations of estradiol and estrone returned to preapplication levels within 24 hours after removal of the system. The estimated daily urinary output of estradiol conjugates increased 5 to 10 times the baseline values and returned to near baseline within 2 days after removal of the system.

By comparison, estradiol (2 mg/day) administered orally to postmenopausal women resulted in increases in mean serum concentration of 59 pg/mL of estradiol and 302 pg/mL of estrone above baseline on the third consecutive day of dosing. Urinary output of estradiol conjugates after oral administration increased to about 100 times the baseline values and did not approach baseline until 7-8 days after the last dose.

In a 3-week multiple-application study of 14 postmenopausal women in which Estraderm 0.05 was applied twice weekly, the mean increments in steady-state serum concentration were 30 pg/mL for estradiol and 12 pg/mL for estrone. Urinary output of estradiol conjugates returned to baseline within 3 days after removal of the last (6th) system, indicating little or no estrogen accumulation in the body.

INDICATIONS AND USAGE

Estraderm® (estradiol transdermal system) is indicated in the following:

1. Treatment of moderate-to-severe vasomotor symptoms associated with menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression that might occur during menopause, and they should not be used to treat these conditions.

2. Treatment of atrophic vaginitis and kraurosis vulvae.

3. Treatment of atrophic urethritis.

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

5. Prevention of osteoporosis (loss of bone mass). The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Estrogen replacement therapy is the most effective single modality for the prevention of postmenopausal osteoporosis in women. Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-controlled studies have shown an approximately 60% reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass for as long as treatment is continued. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. A well-controlled, double-blind, prospective trial conducted at the Mayo Clinic has demonstrated that treatment with Estraderm prevents bone loss in postmenopausal women at a dosage of 0.05 mg/day.

Treatment with Estraderm 0.05 mg showed full maintenance of bone density with a slight (0.8%), but not significant, increase. Placebo treatment resulted in a significant loss of more than 6% below baseline vertebral bone mass. Patients using either Estraderm 0.1 or 0.05 mg had significantly greater bone densities than those using placebo.

Women are at higher risk than men because they have less bone mass, and for several years following natural or induced menopause, the rate of bone mass decline is accelerated. Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton that are associated with osteoporosis include race (white and Asian women are at higher risk than black women); genetic factors (small build, family history); endocrine factors (nulliparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, Type I diabetes); life-style (cigarette smoking, alcohol abuse, sedentary habits); and nutrition (below-average body weight, dietary calcium intake). Calcium deficiency has been implicated in the pathogenesis of the disease. Therefore, when not contraindicated, it is recommended that postmenopausal women receive calcium supplementation.

Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal

type and amount of physical activity that would prevent osteoporosis have not been established.

CONTRAINDICATIONS

Patients with known hypersensitivity to any of the components of the therapeutic system should not use Estraderm.

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

1. Known or suspected pregnancy (see Boxed Warning). Estrogen may cause fetal harm when administered to a pregnant woman.
2. Known or suspected cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders, or a documented history of these conditions.

WARNINGS

1. *Induction of malignant neoplasms.* 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 healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use with increased risks of 15- to 24-fold for 5 to 10 years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study, a significant decrease in the incidence of endometrial cancer occurred 6 months after estrogen withdrawal. Concurrent progestin therapy may offset this risk, but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders. In female offspring, there is an increased risk of vaginal adenosis, squamous cell dysplasia of the cervix, and clear cell vaginal cancer later in life; in males, urogenital and possibly testicular abnormalities. Although some of these changes are benign, it is not known whether they are precursors of malignancy.

2. *Gallbladder disease.* Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in postmenopausal women receiving oral estrogen replacement therapy, similar to the 2-fold increase previously noted in users of oral contraceptives.

3. *Cardiovascular disease.* Large doses of oral 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 risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. It cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

4. *Elevated blood pressure.* Occasional blood pressure increases during postmenopausal estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. Postmenopausal estrogen use does not increase the risk of stroke; nonetheless, blood pressure should be monitored at regular intervals with estrogen use, especially if high doses are used. Ethinyl estradiol and conjugated estrogens have been shown to increase renin substrate. In contrast to these oral estrogens, transdermally administered estradiol does not affect renin substrate.

5. *Hypercalcemia.* Administration of estrogen 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

General

1. *Addition of a progestin.* Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphologic and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes. There are possible additional risks that may be associated with the use of progestins in estrogen replacement regimens. These include (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL), which could diminish the purported cardioprotective effect of estrogen therapy (see PRECAUTIONS, below); (2) impairment of glucose tolerance; and (3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiologic data are available to address this point (see PRECAUTIONS,

below). The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

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 post-menopausal 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. *Physical examination.* A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than 1 year without another physical examination being performed.

4. *Hypercoagulability.* Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. Epidemiological studies, which employed primarily orally administered estrogen products, have suggested that hormone replacement therapy (HRT) may be associated with an increased relative risk of developing venous thromboembolism (VTE), i.e., deep venous thrombosis or pulmonary embolism. Risk/benefit should therefore be carefully weighed in consultation with the patient when prescribing either oral or transdermal HRT to women with a risk factor for VTE.

5. *Familial hyperlipoproteinemia.* Estrogen therapy may be associated with massive elevations of plasma triglycerides, leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

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

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

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

Information for the Patient

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

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. For prevention and treatment of osteoporosis, however, see DOSAGE AND ADMINISTRATION. Tests used to measure adequacy of estrogen replacement therapy include serum estrone and estradiol levels and suppression of serum gonadotropin levels.

Drug/Laboratory Test Interactions

Some of these drug/laboratory test interactions have been observed only with estrogen-progestin combinations (oral contraceptives):

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 beta-thromboglobulin; decreased levels of antifactor 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 T_4 levels determined either by column or by radioimmunoassay. Free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 and free T_3 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 triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.
7. Reduced serum folate concentration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, testis, and liver (see CONTRAINDICATIONS and WARNINGS).

Pregnancy Category X

Estrogens should not be used during pregnancy (see CONTRAINDICATIONS and Boxed Warning).

Nursing Mothers

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

(See WARNINGS regarding induction of neoplasia, adverse effects on the fetus, gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia.)

The most commonly reported adverse reaction to Estraderm in clinical trials was redness and irritation at the application site. This occurred in about 17% of the women treated and caused approximately 2% to discontinue therapy. Reports of rash have been rare. There have also been rare reports of severe systemic allergic reactions.

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

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

2. *Breasts.* Tenderness, enlargement.

3. *Gastrointestinal.* Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; gallbladder disease.

4. *Skin.* Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.

5. *Eyes.* Steepening of corneal curvature; intolerance to contact lenses.

6. *CNS.* Headache, migraine, dizziness; mental depression; chorea.

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

ACUTE 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 Estraderm system should be placed on a clean, dry area of the skin on the trunk of the body (including the buttocks and abdomen). The site selected should be one that is not exposed to sunlight. *Estraderm should not be applied to the breasts.* The Estraderm system should be replaced twice weekly. 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 the system off. 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 palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the unlikely event that a system should fall off, the same system may be reapplied. If necessary, a new system may be applied. In either case, the original treatment schedule should be continued.

Initiation of Therapy

Estraderm is currently available in two dosage forms – 0.05 mg and 0.1 mg. For treatment of moderate-to-severe vasomotor symptoms, atrophic vaginitis, and atrophic urethritis associated with menopause, initiate therapy with Estraderm 0.05 applied to the skin twice weekly. The lowest dose that will control symptoms should be chosen, and medication should be discontinued as promptly as possible. Attempts to discontinue or taper medication given only for these menopausal symptoms should be made at 3-month to 6-month intervals.

Prophylactic therapy with Estraderm to prevent postmenopausal bone loss should be initiated with the 0.05 mg/day dosage as soon as possible after menopause. The dosage may be adjusted if necessary. Discontinuation of estrogen replacement therapy may reestablish bone loss at a rate comparable to the immediate postmenopausal period.

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

Therapeutic Regimen

Estraderm therapy may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, Estraderm may be given on a cyclic schedule (e.g., 3 weeks on drug followed by 1 week off drug).

HOW SUPPLIED

Estraderm estradiol transdermal system 0.05 mg/day – each 10 cm^2 system contains 4 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.
Patient Calendar Pack of 8 Systems.....NDC 0083-2310-08
Carton of 6 Patient Calendar Packs of 8 Systems.....NDC 0083-2310-62
Carton of 1 Patient Calendar Pack of 24 Systems .....NDC 0083-2310-24

Estraderm estradiol transdermal system 0.1 mg/day – each 20 cm^2 system contains 8 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.
Patient Calendar Pack of 8 Systems.....NDC 0083-2320-08
Carton of 6 Patient Calendar Packs of 8 Systems.....NDC 0083-2320-62
Carton of 1 Patient Calendar Pack of 24 Systems .....NDC 0083-2320-24

*See DESCRIPTION.

Do not store above 30°C (86°F).

Do not store unpouched. Apply immediately upon removal from the protective pouch.

Information for the Patient

Estraderm®
Generic name: estradiol transdermal system
pronounced ess-tra-DYE-all

Rx only

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.

INTRODUCTION

Your doctor has prescribed Estraderm for the treatment of your menopausal symptoms and/or to prevent osteoporosis. During menopause, production of estrogen hormones by your body decreases well below the amounts normally produced during your fertile years. In many women, this decrease in estrogen production causes uncomfortable symptoms, most noticeably, hot flushes and sleep disturbance. Estrogens can be given to reduce or eliminate these symptoms and/or to prevent osteoporosis.

The Estraderm 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. Your doctor will prescribe the lowest dose you require, depending upon your individual response. The dose is adjusted by the size of the Estraderm system used; the systems are available in two sizes. The length of treatment will depend on the reason for use.

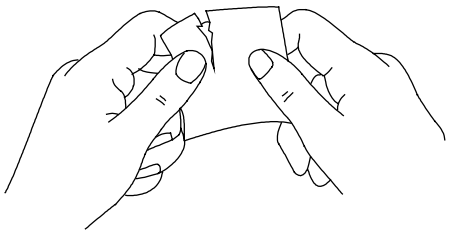
INFORMATION ABOUT ESTRADERM

How Estraderm Works

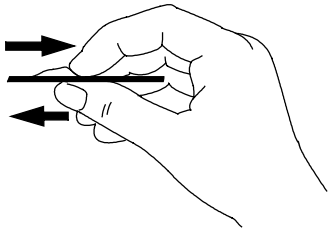
Estraderm contains estradiol. When applied to the skin as directed below, the Estraderm system releases estradiol, which flows through the skin into the bloodstream.

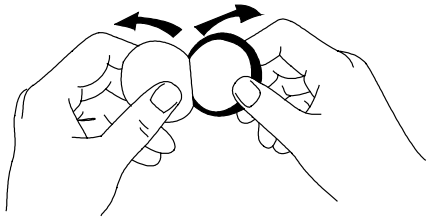
How and Where to Apply Estraderm

Each Estraderm system is individually sealed in a protective pouch. Tear open this pouch at the indentation (do not use scissors) and remove the system. Bubbles in the system are normal.

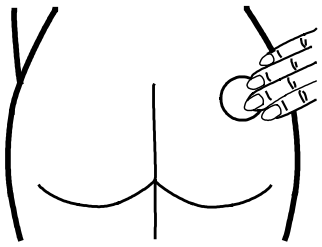


A stiff protective liner covers the adhesive side of the system — the side that will be placed against your skin. This liner must be removed before applying the system. Slide the protective liner sideways between your thumb and index finger. Then hold the system at one edge. Remove the protective liner and discard it. Try to avoid touching the adhesive.





Apply the adhesive side of the system to a clean, dry area of the skin on the trunk of the body (including the buttocks and abdomen).



The site selected should be one that is not exposed to sunlight. Some women may find that it is more comfortable to wear Estraderm on the buttocks. *Do not apply Estraderm 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 the system off. Apply the system

immediately after opening the pouch and removing the protective liner. Press the system firmly in place with the palm of your hand for about 10 seconds, making sure there is good contact, especially around the edges.

The Estraderm system should be worn continuously until it is time to replace it with a new system. 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 Estraderm

The Estraderm system should be replaced twice weekly. Your Estraderm package contains a calendar checklist on the back to help you remember a schedule. Mark the 2-day schedule you plan to follow. Always change the system on the 2 days of the week you have marked.

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

Please note: 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, put this same system back on and continue to follow your original treatment schedule. If necessary, you may apply a new system but continue to follow your original schedule.

Benefits of Treatment With Estraderm

Regular use of Estraderm twice weekly offers relief of moderate-to-severe symptoms of menopause and has been shown to help prevent osteoporosis, which is a thinning of the bones that makes them more fragile. In the years following the menopause, unless estrogen therapy is taken regularly, your bones can rapidly lose strength, possibly leading to osteoporosis and bone fractures. Estraderm may prevent this bone loss and the development of osteoporosis and may help you to avoid fractures of your spine ("dowager's hump"), wrist, and hip later in life.

Small quantities of the naturally occurring hormone estradiol are absorbed through the skin from the Estraderm system, ensuring a continuous supply of circulating hormone in the body.

There is no medical evidence that the use of any estrogen during menopause will keep you feeling young, keep your skin soft, or relieve nervousness.

USES OF ESTROGEN

To reduce moderate-to-severe menopausal symptoms. Estrogens are hormones produced by the ovaries. The decrease in the amount of estrogen that occurs in all women, usually between ages 45 and 55, causes the menopause. Sometimes the ovaries are removed by an operation, causing "surgical menopause." When the amount of estrogen begins to decrease, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck,

and chest or sudden intense episodes of heat and sweating ("hot flashes"). The use of drugs containing estrogens can help the body adjust to lower estrogen levels.

Some women have only mild menopausal symptoms, or none at all, and do not need estrogen therapy for these particular symptoms. Other women may need estrogens for a few months while their bodies adjust to lower estrogen levels. For the treatment of menopausal symptoms only, most women need estrogen replacement therapy for no longer than 6 months. The prevention of osteoporosis may require longer-term therapy.

To prevent osteoporosis (brittle bones). After age 40, and especially after menopause, women begin to lose bone more rapidly, and some women develop osteoporosis. This thinning of the bones makes the bones weaker and more likely to break, often leading to fractures of the spine, hip, and wrist. Taking estrogens after the menopause slows down or halts bone loss and may prevent bones from breaking. Rapid loss of bone may begin soon after estrogen therapy is discontinued. Eating foods that are high in calcium (such as milk products) or taking calcium supplements and certain types of exercise may also help prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these life-style changes with your doctor to find out if they are safe for you. Since estrogen use is associated with some risk, its use in the prevention of osteoporosis should be confined to women who appear to be susceptible to this condition. The following characteristics are often present in women who are likely to develop osteoporosis: early menopause; white or Asian race; a family history of osteoporosis in a mother, sister, or aunt; slight build; cigarette smoking; alcohol abuse; or sedentary life-style.

Women who had their menopause by the surgical removal of their ovaries at a relatively young age may be good candidates for Estraderm therapy to help prevent osteoporosis.

To treat atrophic vaginitis (itching, burning, dryness in or around the vagina) *and atrophic urethritis* (which may cause difficulty or burning on urination).

WHEN ESTROGENS SHOULD NOT BE USED

During pregnancy. Although the possibility is fairly small, there is a greater risk of having a child born with a birth defect if you take estrogens during pregnancy. A male child may have an increased risk of developing abnormalities of the urinary system and sex organs. A female child may have an increased risk of developing cancer of the vagina or cervix in her teens or twenties. Estrogen is not effective in preventing miscarriage (abortion). In addition, estrogen should not be used after childbirth to prevent the breasts from filling with milk, or while breast-feeding.

If you have undiagnosed vaginal bleeding. Unusual vaginal bleeding can be a warning sign of uterine cancer, especially if it happens after menopause. Your doctor must find out the proper treatment, if any. 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 any circulation problems. Estrogen therapy should be used only after consultation with your doctor and only in recommended doses. Patients with a tendency for abnormal blood clotting should avoid estrogen use (see DANGERS OF ESTROGENS).

If you have had cancer. Since estrogens increase the risk of certain cancers, you should not take estrogens if you have ever had cancer of the breast or uterus.

When they are ineffective. Sometimes women experience nervous symptoms or depression during menopause. There is no evidence that estrogens are effective for such symptoms. You may have heard that taking estrogens for long periods (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 treatment may carry serious risks.

DANGERS OF ESTROGENS

Cancer of the uterus. The risk of cancer of the uterus increases the longer estrogens are used and when larger doses are taken. One study showed that when estrogens are discontinued, this increased risk of cancer seems to fall off quickly. Three other studies showed that the risk for uterine cancer stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, *it is important to take the lowest dose of estrogen that will control your symptoms 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 (see OTHER INFORMATION).

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 healthcare 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 increase the risk of blood clots. These clots can cause a stroke, heart attack, or pulmonary embolus, any of which may be fatal.

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 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.
- Skin irritation, redness, or rash may occur at the site of Estraderm application.

REDUCING RISK OF ESTROGEN USE

If you decide to take estrogen replacement therapy, you can reduce your risks by carefully monitoring your treatment.

See your doctor regularly. While you are taking estrogens, it is important that you visit your doctor at least once a year for a physical examination. If members of your family have had breast cancer or if you have ever had breast nodules or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

Reevaluate your need for estrogens. You and your doctor should reevaluate your need for estrogens at least every 6 months.

Be alert for signs of trouble. Report these or any other unusual side effects to your doctor immediately:

- Abnormal bleeding from the vagina.
- Pains in the calves or chest, a sudden shortness of breath, or coughing blood (indicating possible clots in the legs, heart, or lungs).
- Severe headache, dizziness, faintness, or changes in vision, indicating possible clots in the brain or eye.
- Breast lumps.
- Yellowing of the skin.
- Pain, swelling, or tenderness in the abdomen.
- Skin irritation, redness, or rash.

OTHER INFORMATION

If your uterus has not been removed, your doctor may choose to prescribe a progestin, a different hormonal drug, to be used in association with estrogen treatment. Progestins lower the risk of developing endometrial hyperplasia, a possible precancerous condition of the uterine lining, which may occur while using estrogens. There are possible additional risks that may be associated with the inclusion of a progestin in estrogen treatment. The possible risks include unfavorable effects on blood fats and sugars, as well as a possible further increase in breast cancer risk that may be associated with long-term estrogen use.

Some research has suggested that estrogens taken without progestins may protect women against developing heart disease. However, this effect of estrogens is not certain.

You are cautioned to discuss very carefully with your doctor or healthcare provider all the possible risks and benefits of long-term estrogen and progestin treatment, as they affect you personally.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about the amounts recommended.

Keep this and all drugs out of the reach of children. In case of overdose, remove the Estraderm system and call your doctor, hospital, or poison control center immediately.

This leaflet provides the most important information about estrogens. If you want to read more, ask your doctor or pharmacist to let you read the professional labeling.

T2000-61/T2000-62

REV: SEPTEMBER 2000 Printed in U.S.A. 89009702

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936