



**Estraderm<sup>®</sup>**

**(estradiol transdermal system)**

**Rx only**

**WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA**

**Estrogen-Alone Therapy**

**Endometrial Cancer**

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. (See **WARNINGS, Malignant Neoplasms, Endometrial Cancer.**)

**Cardiovascular Disorders and Probable Dementia**

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders and Probable Dementia.**)

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders.**)

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use.**)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

**Estrogen Plus Progestin Therapy**

**Cardiovascular Disorders and Probable Dementia**

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders and Probable Dementia.**)

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary emboli (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders.**)

The WHIMS estrogen plus progestin ancillary study of the WHI reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) plus MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use.**)

### Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. (See **CLINICAL STUDIES** and **WARNINGS, Malignant Neoplasms, Breast Cancer.**)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

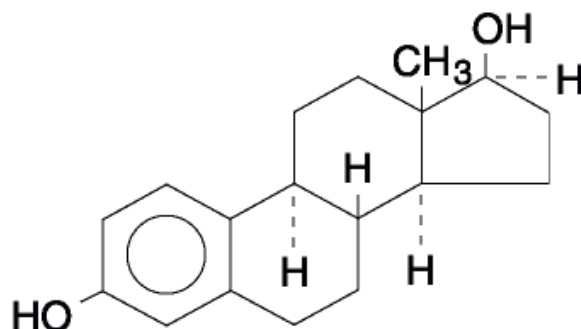
## DESCRIPTION

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 percent). Each corresponding system having an active surface area of 10 or 20 cm<sup>2</sup> 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.

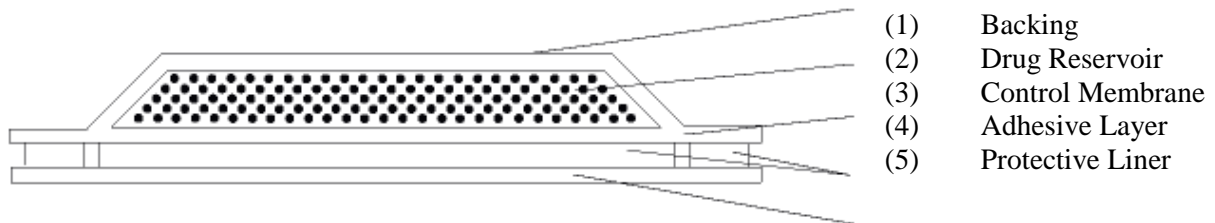
Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5 (10)-triene-3,17 $\beta$ -diol.

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/ethylene vinyl acetate copolymer film, (2) a drug reservoir of estradiol USP and alcohol USP gelled with

hydroxypropyl cellulose NF, (3) an ethylene-vinyl acetate copolymer membrane, and (4) an adhesive formulation of light mineral oil NF and polyisobutylene. A protective liner (5) of siliconized 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 estradiol. The remaining components of the system are pharmacologically inactive. Alcohol is also released from the system during use.

## CLINICAL PHARMACOLOGY

Endogenous 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  $\mu\text{g}$  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 in the 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, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

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

The skin metabolizes estradiol only to a small extent. In contrast, orally administered estradiol is rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels of estrone than estradiol. Therefore, transdermal administration produces therapeutic plasma levels of estradiol with lower circulating levels of estrone and estrone conjugates and requires smaller total doses than does oral therapy.

#### A. Absorption

Administration of Estraderm (estradiol transdermal system) 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 per 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 to 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.

#### B. 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. Estrogens circulate in the blood largely bound to sex hormone-binding globulin (SHBG) and albumin.

#### C. 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 by Cytochrome 450 isoforms CYP1A2 and CYP3A4. Estradiol undergoes further metabolism to sulfate and glucuronide conjugates. Estradiol and its metabolites are glucuronidated by UGT1A1 and UGT2B7. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a 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 intestine 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.

#### D. Excretion

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

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, for example, in a cycling regimen.

#### E. Special Populations

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

#### F. Drug Interactions

*In vitro* and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

### CLINICAL STUDIES

#### Effects on Vasomotor Symptoms

Two clinical trials were designed to assess the relief of moderate to severe vasomotor symptoms among postmenopausal female patients. The first trial evaluated the efficacy of Estraderm (estradiol) Transdermal Therapeutic System (TTS), in controlling the frequency of postmenopausal hot flushes. The study had two phases. Phase 1 was a randomized, double-blind, parallel-group design study involving two groups of patients (n=30). Group 1 received a transdermal placebo patch and Group 2 received Estraderm patches with an estradiol release rate of 0.10 mg per day. In Phase 2, a third group of patients received Estraderm patches with an estradiol release rate of 0.05 mg per day, on a single-blind basis. A placebo control was not included in this phase of the study. In both phases, each patient received a 21-day treatment of the assigned medication.

Baseline laboratory values for endogenous reproductive hormones, including estradiol / estrone serum levels, Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) were collected and analyzed at the end of the 21-day treatment period.

The mean ( $\pm$  standard error of the mean) hourly frequency of hot flushes were significantly reduced with Estraderm decreasing from  $0.79 \pm 0.08$  flushes per hour to  $0.35 \pm 0.10$  flushes per hour in patients treated with Estraderm 0.05 mg per day, at the end of the 21-day treatment period. In patients treated with Estraderm 0.10 mg per day, hot flushes were significantly decreased from  $0.65 \pm 0.06$  flushes per hour to  $0.21 \pm 0.09$  flushes per hour. There was no significant mean difference in the placebo-treated group,  $0.87 \pm 0.10$  flushes per hour and  $0.88 \pm 0.10$  flushes per hour, respectively.

Both Estraderm TTS 0.05 mg per day and 0.10 mg per day showed an increase from baseline in circulating levels of estradiol (E2), estrone (E1) and the E2/E1 ratio, showing restoration of levels to an early and mid-follicular premenopausal state.

Both FSH and LH levels displayed a decrease from baseline similar to levels seen prior to menopause.

The second clinical trial was a double-blind, randomized, comparative study designed to subjectively evaluate the efficacy of Estraderm (estradiol) Transdermal Therapeutic System (TTS), in comparison with an oral active comparator in patients whose menopausal symptoms were currently well controlled by the active comparator 0.625 mg or 1.25 mg (n=124). All patients were to either have been oophorectomized 3 months prior to enrollment or had a last menstrual period 6 months prior to enrollment. Of the women enrolled, 75 percent had undergone a previous oophorectomy.

The efficacy of the treatment in this study were determined by (daily recording by the patient of the number and severity of hot flushes and daily recording by the patient of the five menopausal symptoms (sweating, headache, insomnia, vaginal discomfort and urge to urinate).

The average number of hot flushes over weeks 1, 2 and 3 were compared to the average number of hot flushes over weeks 5, 6 and 7. In no instances were any of the differences significant between Estraderm TTS and the orally administered active comparator, either for the oophorectomized patients or the entire group.

### **Effects on Postmenopausal Osteoporosis**

Two clinical trials were designed to assess Estraderm (estradiol) Transdermal Therapeutic System (TTS) for the prevention and treatment of osteoporosis respectively, in postmenopausal female patients.

The first study was designed to evaluate Estraderm for the prevention of osteoporotic changes among women whom had undergone an oophorectomy/hysterectomy within 2 years of study entry and have not been estrogen deprived for more than 6 months since surgery. This was a 2 year prospective, randomized, parallel-group, stratified (by age group: 40-49 years,  $\geq 50$  years), double-blind study (n=95) comparing three Estraderm dosages (0.025, 0.05 and 0.10 mg per day) in a pooled analysis versus placebo. The primary efficacy variable was percent change in bone mineral density (BMD) as measured by Dual Photon Absorptiometry (DPA) of the lumbar spine (L2-L4).

The mean percentage changes in BMD were +3.66, +0.82, and -2.95 g/cm<sup>2</sup>, for Estraderm 0.10 mg per day, 0.05 mg per day, and 0.025 mg per day, respectively, and each was significantly different from the mean for placebo group (-6.42). The primary objective of the second clinical trial was to determine the efficacy of Estraderm (estradiol) Transdermal Therapeutic System (TTS) used in a cyclical regimen in conjunction with oral medroxyprogesterone acetate (MPA) for the prevention of further loss of BMD and new/worsened vertebral fractures in postmenopausal women with osteoporosis and evidence of prior vertebral fractures. During this 12-month, double-blind, parallel group, placebo-controlled trial, patients were randomized into two different treatment groups. The active treatment group received the following cyclical regimen: Estraderm 0.1 mg per day on days 1-22 of each 28 day cycle, corresponding to 6 patches worn 3.5 days each, together with MPA 10 mg tablets taken orally, once daily on days 13-22. No medications were prescribed on day 23-28. The control group received matched placebos for both Estraderm TTS and the MPA 10 mg tablet.

The primary efficacy variable was percent change in BMD of the lumbar vertebrae (L2-L4) utilizing Dual Photon Absorptiometry (DPA) after 1 year of treatment. Estraderm 0.10 mg per day taken with MPA was shown to significantly increase mean bone density after 6 months

and 12 months of treatment +4.0 percent and +7.5 percent, respectively. Only nominal changes (<1 percent) were seen in the placebo group.

### Women’s Health Initiative Studies

The Women’s Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease [(CHD) defined as nonfatal MI, silent MI and CHD death], with invasive breast cancer as the primary adverse outcome. A “global index” included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in CE and MPA substudy), colorectal cancer, hip fracture, or death due to other causes. These substudies did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms.

#### *WHI Estrogen-Alone Substudy*

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints. Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in Table 1.

**TABLE 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI<sup>a</sup>**

Event	Relative Risk CE vs. Placebo (95% nCI <sup>b</sup> )	CE n = 5,310 Absolute Risk per 10,000 Women-Years	Placebo n = 5,429
CHD Events <sup>c</sup>	0.95 (0.78-1.16)	54	57
<i>Non-fatal MI<sup>c</sup></i>	<i>0.91 (0.73-1.14)</i>	<i>40</i>	<i>43</i>
<i>CHD death<sup>c</sup></i>	<i>1.01 (0.71-1.43)</i>	<i>16</i>	<i>16</i>
All strokes <sup>c</sup>	1.33 (1.05-1.68)	45	33
<i>Ischemic stroke<sup>c</sup></i>	<i>1.55 (1.19-2.01)</i>	<i>38</i>	<i>25</i>
Deep vein thrombosis <sup>c,d</sup>	1.47 (1.06-2.06)	23	15
Pulmonary embolism <sup>c</sup>	1.37 (0.90-2.07)	14	10
Invasive breast cancer <sup>c</sup>	0.80 (0.62-1.04)	28	34
Colorectal cancer <sup>e</sup>	1.08 (0.75-1.55)	17	16
Hip fracture <sup>c</sup>	0.65 (0.45-0.94)	12	19
Vertebral fractures <sup>c,d</sup>	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures <sup>c,d</sup>	0.58 (0.47-0.72)	35	59
Total fractures <sup>c,d</sup>	0.71 (0.64-0.80)	144	197
Death due to other causes <sup>e,f</sup>	1.08 (0.88-1.32)	53	50
Overall mortality <sup>c,d</sup>	1.04 (0.88-1.22)	79	75
Global Index <sup>g</sup>	1.02 (0.92-1.13)	206	201

<sup>a</sup>Adapted from numerous WHI publications. WHI publications can be viewed at

www.nhlbi.nih.gov/whi.

<sup>b</sup> Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

<sup>c</sup> Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

<sup>d</sup> Not included in “global index”.

<sup>e</sup> Results are based on an average follow-up of 6.8 years.

<sup>f</sup> All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

<sup>g</sup> A subset of the events was combined in a “global index”, defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI “global index” that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures. The absolute excess risk of events included in the “global index” was a nonsignificant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess was present in all subgroups of women examined.

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50 to 59 years of age, a non-significant trend toward reduced risk for CHD [hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)] and overall mortality [HR 0.71 (95 percent CI, 0.46-1.11)].

#### *WHI Estrogen Plus Progestin Substudy*

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the “global index”. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years.

For those outcomes included in the WHI “global index” that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.



Results of the estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other), are presented in Table 2. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

**TABLE 2. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN PLUS PROGESTIN SUBSTUDY OF WHI AT AN AVERAGE OF 5.6 YEARS<sup>a,b</sup>**

Event	Relative Risk	CE/MPA	Placebo
	CE/MPA vs. Placebo (95% nCI <sup>c</sup> )	n = 8,506	n = 8,102
Absolute Risk per 10,000 Women-Years			
CHD Events	1.23 (0.99-1.53)	41	34
<i>Non-fatal MI</i>	<i>1.28 (1.00-1.63)</i>	<i>31</i>	<i>25</i>
<i>CHD death</i>	<i>1.10 (0.70-1.75)</i>	<i>8</i>	<i>8</i>
All strokes	1.31 (1.03-1.68)	33	25
<i>Ischemic stroke</i>	<i>1.44 (1.09-1.90)</i>	<i>26</i>	<i>18</i>
Deep vein thrombosis <sup>d</sup>	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer <sup>e</sup>	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer <sup>d</sup>	0.81 (0.48-1.36)	6	7
Cervical cancer <sup>d</sup>	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures <sup>d</sup>	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures <sup>d</sup>	0.71 (0.59-0.85)	44	62
Total fractures	0.76 (0.69-0.83)	152	199
Overall Mortality <sup>f</sup>	1.00 (0.83-1.19)	52	52
Global Index <sup>g</sup>	1.13 (1.02-1.25)	184	165

<sup>a</sup> Adapted from numerous WHI publications. WHI publications can be viewed at [www.nhlbi.nih.gov/whi](http://www.nhlbi.nih.gov/whi).

<sup>b</sup> Results are based on centrally adjudicated data.

<sup>c</sup> Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

<sup>d</sup> Not included in “global index”.

<sup>e</sup> Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.

<sup>f</sup> All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

<sup>g</sup> A subset of the events was combined in a “global index”, defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy

stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for overall mortality [HR 0.69 (95 percent CI, 0.44-1.07)].

### **Women's Health Initiative Memory Study**

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

The WHIMS estrogen plus progestin ancillary study enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years of age; 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

## **INDICATIONS AND USAGE**

Estraderm is indicated in:

1. Treatment of moderate to severe vasomotor symptoms due to menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400 to 800 IU per day may also be required to ensure adequate daily intake in postmenopausal women.

## **CONTRAINDICATIONS**

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

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected or history of breast cancer.
3. Known or suspected estrogen-dependent neoplasia.
4. Active DVT, PE, or a history of these conditions.
5. Active arterial thromboembolic disease (for example, stroke and myocardial infarction) or a history of these conditions.
6. Known anaphylactic reaction or angioedema or hypersensitivity to Estraderm.
7. Known liver impairment or disease.
8. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.
9. Known or suspected pregnancy.

## **WARNINGS**

See **BOXED WARNING**.

1. Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy.

An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy.

Should any of these events occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). (See **CLINICAL STUDIES**.) The increase in risk was demonstrated in year 1 and persisted. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years). (See **CLINICAL STUDIES**.) The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

b. Coronary heart disease

In the WHI estrogen-alone substudy, no overall effect on CHD events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo. (See **CLINICAL STUDIES**.)

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women less than 10 years since menopause (8 versus 16 per 10,000 women-years).

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5.

In postmenopausal women with documented heart disease (n=2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred twenty-one (2,321) women from the

original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and in the placebo group in HERS, HERS II, and overall.

c. Venous thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to women receiving placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years. (See **CLINICAL STUDIES**.) Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See **CLINICAL STUDIES**.) Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant Neoplasms

a. Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-times 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 the 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, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg)-alone was not

associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80). (See **CLINICAL STUDIES**.)

- The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups. (See **CLINICAL STUDIES**.)

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

#### c. Ovarian cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer.

The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

### 3. Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use.**)

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use.**)

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **PRECAUTIONS, Geriatric Use.**)

### 4. Gallbladder Disease

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

### 5. Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

### 6. Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a

sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

#### 7. Anaphylactic Reaction and Angioedema

Cases of anaphylaxis, which developed anytime during the course of Estraderm treatment and required emergency medical management, have been reported in the postmarketing setting. Skin (hives, pruritis, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) involvement has been noted.

Angioedema involving the tongue, larynx, face, hands and feet requiring medical intervention has occurred postmarketing in patients using Estraderm. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop an anaphylactic reaction with or without angioedema after treatment with Estraderm should not receive Estraderm again.

#### 8. Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

## **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 with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

#### 2. Elevated blood pressure

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

#### 3. Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

#### 4. Hepatic impairment and/or past history of cholestatic jaundice

Although transdermally administered estrogen therapy avoids first-pass hepatic metabolism, estrogens may be poorly metabolized in patients with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.



## 5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T<sub>4</sub> and T<sub>3</sub> serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

## 6. Fluid retention

Estrogens may cause some degree of fluid retention. Women with conditions which might be influenced by this factor, such as cardiac or renal impairment, warrant careful observation when estrogens are prescribed.

## 7. Hypocalcemia

Estrogen therapy should be used with caution in individuals with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

## 8. Exacerbation of endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

## 9. Exacerbation of other conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

## B. Patient Information

Physicians are advised to discuss the content of the **PATIENT INFORMATION** leaflet with patients for whom they prescribe Estraderm.

## C. Laboratory Tests

Serum FSH and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

Laboratory parameters may be useful in guiding dosage for the treatment of hypoestrogenism due to hypogonadism, castration and primary ovarian failure.

## 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 beta-thromboglobulin; 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 TBG leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T<sub>4</sub> levels (by column or by radioimmunoassay) or T<sub>3</sub> levels by radioimmunoassay. T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG. Free T<sub>4</sub> and free T<sub>3</sub> concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.
  3. Other binding proteins may be elevated in serum, for example, corticosteroid-binding globulin (CBG), SHBG, leading to increased circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
  4. Increased plasma high density lipoprotein (HDL) and HDL<sub>2</sub> cholesterol subfraction concentrations, reduced low density protein (LDL) cholesterol concentration, increased triglycerides levels.
  5. Impaired glucose tolerance.
- E. 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, uterus, cervix, vagina, testis, and liver.

F. Pregnancy

Estraderm should not be used during pregnancy. (See **CONTRAINDICATIONS**.) There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

G. Nursing Mothers

Estraderm should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogens. Caution should be exercised when Estraderm is administered to a nursing woman.

H. Pediatric Use

Estrogen 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.

I. Geriatric Use

There have not been sufficient numbers of geriatric women involved in studies utilizing Estraderm to determine whether those over 65 years of age differ from younger subjects in their response to Estraderm.

#### *The Women's Health Initiative Studies*

- In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age. (See **CLINICAL STUDIES**.)

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo) there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age. (See **CLINICAL STUDIES**.)

#### *The Women's Health Initiative Memory Study*

- In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia**.)

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia**.)

## **ADVERSE REACTIONS**

See **BOXED WARNING, WARNINGS** and **PRECAUTIONS**.

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

### **Postmarketing Experience**

The following additional adverse reactions have been identified during post-approval use of Estraderm. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

#### Genitourinary System

Breakthrough bleeding, spotting, endometrial hyperplasia, uterine leiomyomata.

#### Breast

Breast cancer, discomfort, pain, tenderness.

#### Cardiovascular

Hypertension, varicose veins, pulmonary embolism.

#### Gastrointestinal

Abdominal pain, abdominal distension, abnormal liver tests, jaundice cholestatic, nausea, vomiting, diarrhea, cholelithiasis, gall bladder disorder.

#### Skin

Alopecia, contact dermatitis, pigmentation disorders, cholasma, melasma, pruritus.

#### Central Nervous System

Affect lability, dizziness, depression, nervousness, libido disorder, headache, migraine.

#### Miscellaneous

Back pain, extremity pain, edema, hypersensitivity, libido disorder, increase or decrease in weight.

Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

## **OVERDOSAGE**

Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of Estraderm therapy with institution of appropriate symptomatic care.

## **DOSAGE AND ADMINISTRATION**

The adhesive side of the Estraderm transdermal 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 transdermal system should be applied immediately after opening the pouch and removing the protective liner. The transdermal 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 transdermal 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

When estrogen therapy is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen-alone or in combination with a progestin, should be with the lowest effective dose and the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (for example, 3-month to 6-month intervals) to determine whether treatment is still necessary. Adequate diagnostic measures, such as directed or random endometrial

sampling, when indicated, should be undertaken to rule out malignancy in a postmenopausal woman with a uterus with undiagnosed persistent or recurring abnormal genital bleeding.

Estraderm is currently available in two dosage forms – 0.05 mg and 0.1 mg. Patients should be started at the lowest dose. The lowest effective dose of Estraderm has not been determined.

For treatment of moderate to severe vasomotor symptoms or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause, initiate therapy with Estraderm 0.05 applied to the skin twice weekly.

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 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 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 (for example, 3 weeks on drug followed by 1 week off drug).

## HOW SUPPLIED

*Estraderm estradiol transdermal system 0.05 mg per day* – each 10 cm<sup>2</sup> 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 0078-0480-42

*Estraderm estradiol transdermal system 0.1 mg per day* – each 20 cm<sup>2</sup> 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 0078-0481-42

---

\*See DESCRIPTION.

Do not store above 30°C (86°F).

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

T2017-88  
November2017

## Patient Information

### Estraderm<sup>®</sup>

#### (estradiol transdermal system)

Read this PATIENT INFORMATION before you start using the Estraderm patch and read all the information that you get each time you refill your Estraderm prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

#### **What is the most important information I should know about Estraderm (an estrogen hormone)?**

- Using estrogen-alone increases your chance of getting cancer of the uterus (womb).  
Report any unusual vaginal bleeding right away while you are using Estraderm. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes, or dementia (decline of brain function)
- Using estrogen-alone may increase your chances of getting strokes or blood clots
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age or older
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots
- Using estrogens with progestin may increase your chance of getting dementia, based on a study of women 65 years of age or older
- You and your healthcare provider should talk regularly about whether you still need treatment with Estraderm

#### **What is Estraderm?**

Estraderm is a patch that contains the estrogen hormone, estradiol. When applied to the skin as directed below, Estraderm releases estrogen through the skin into the bloodstream.

#### **What is Estraderm used for?**

Estraderm is used after menopause to:

- **Reduce moderate to severe hot flashes.**

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes,

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 strong feelings of heat and sweating (“hot flashes” or “hot flushes”). In some women the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe.

- **Treat menopausal changes in or around the vagina.**

You and your healthcare provider should talk regularly about whether you still need treatment with Estraderm to control these problems. If you use Estraderm only to treat your menopausal changes in or around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

- **Treat certain conditions in women before menopause if their ovaries do not produce enough estrogens naturally.**
- **Help reduce your chances of getting osteoporosis (thin weak bones).**

Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use Estraderm only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

Weight-bearing exercise, like walking or running, and taking calcium (1500 mg per day of elemental calcium) and vitamin D (400 to 800 IU per day) supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

You and your healthcare provider should talk regularly about whether you should continue treatment with Estraderm.

### **Who should not use Estraderm?**

Do not start using Estraderm if you:

- **Have unusual vaginal bleeding**
- **Currently have or have had certain cancers**

Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use Estraderm.

- **Had a stroke or heart attack**
- **Currently have or have had blood clots**
- **Currently have or have had liver problems**
- **Have been diagnosed with a bleeding disorder**
- **Are allergic to Estraderm or any of its ingredients**

See the list of ingredients in Estraderm at the end of this leaflet.

- **Think you may be pregnant**

## **Tell your healthcare provider:**

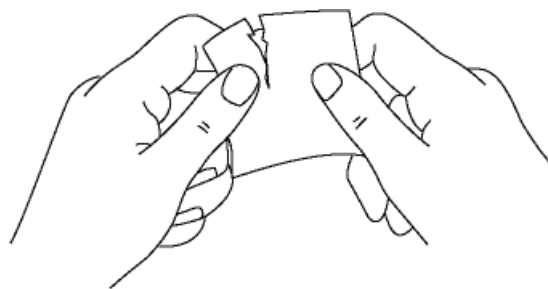
- **If you have any unusual vaginal bleeding.**  
Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **About all of your medical problems**  
Your healthcare provider may need to check you more carefully if you have certain conditions such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **About all the medicines you take**  
This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Estraderm works. Estraderm may also affect how other medicines work.
- **If you are going to have surgery or will be on bed rest**  
You may need to stop using Estraderm.
- **If you are breast feeding**  
The hormone in Estraderm can pass into your breast milk.

## **How should I use Estraderm?**

1. Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.
2. Estrogens should be used at the lowest dose possible for your treatment, only as long as needed. The lowest effective dose of Estraderm has not been determined. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are using and whether you still need treatment with Estraderm.

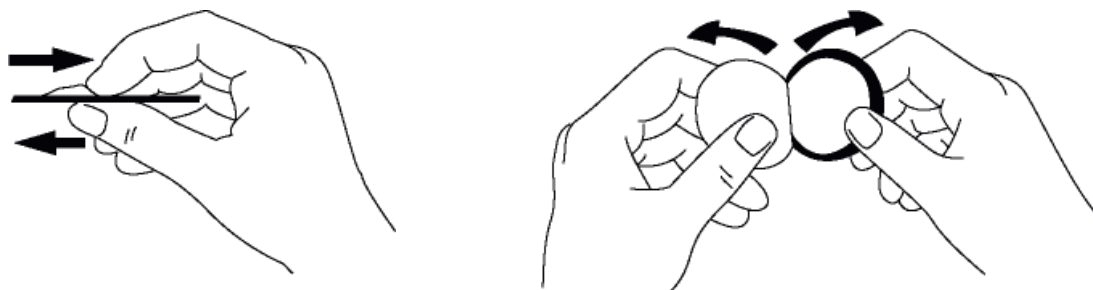
## **How and where to apply Estraderm**

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 patch are normal.



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





Apply the adhesive side of the patch 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 patch off. Apply the patch immediately after opening the pouch and removing the protective liner. Press the patch 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 patch should be worn continuously until it is time to replace it with a new patch. You may wish to experiment with different locations when applying a new patch, to find ones that are most comfortable for you and where clothing will not rub on the patch.

### ***When to Apply Estraderm***

The Estraderm patch 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 patch on the 2 days of the week you have marked.

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

Please note: Contact with water when you are bathing, swimming, or showering will not affect the patch. In the unlikely event that a patch should fall off, put this same patch back on and continue to follow your original treatment schedule. If necessary, you may apply a new patch but continue to follow your original schedule.

### **What are the possible side effects of Estraderm?**

**Side effects are grouped by how serious they are and how often they happen when you are treated.**

**Serious, but less common side effects include:**

- Heart attack
- Stroke
- Blood clots
- Dementia
- Breast cancer
- Cancer of the lining of the uterus (womb)
- Cancer of the ovary
- High blood pressure
- High blood sugar
- Gallbladder disease
- Liver problems
- Enlargement of benign tumors of the uterus (“fibroids”)
- Severe allergic reactions

**Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:**

- New breast lumps
- Unusual vaginal bleeding
- Changes in vision or speech
- Sudden new severe headaches
- Severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- Swollen lips, tongue and face

**Less serious, but common side effects include:**

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach or abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

These are not all the possible side effects of Estraderm. For more information, ask your healthcare provider or pharmacist for advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **What can I do to lower my chances of getting a serious side effect with Estraderm?**

- Talk with your healthcare provider regularly about whether you should continue using Estraderm
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the uterus (womb)
- See your healthcare provider right away if you get vaginal bleeding while using Estraderm.
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

### **General information about the safe and effective use of Estraderm**

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

### **Keep Estraderm out of the reach of children.**

This leaflet provides a summary of the most important information about Estraderm. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Estraderm that is written for health professionals. You can get more information by calling the toll-free number (888-NOW-NOVA (888-669-6682).

### **What are the ingredients in Estraderm?**

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

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



Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey 07936

© Novartis

T2017-88/T2012-139  
November 2017/July 2012