

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-081/S-036 & S-039

Trade Name: Estraderm 0.05 mg/day, 0.1 mg/day

Generic Name: estradiol transdermal system

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: May 28, 2004

Indications: For the treatment of moderate to severe vasomotor symptoms associated with the menopause; the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause; treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; and prevention of postmenopausal osteoporosis.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-081/S-036 & S-039

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-081/S-036/S-039

Novartis Pharmaceuticals Corporation
Attention: Kevin M. Carl, PharmD.
Assistant Director
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Carl:

Please refer to your supplemental new drug applications (S-036) dated November 22, 2002, received November 25, 2002, and (S-039) dated October 2, 2003, received October 3, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estraderm® (estradiol transdermal system).

We also acknowledge receipt of your submissions dated March 18, 2003, and January 16, 2004, amendments to supplement 036.

Supplement 036 provides for multiple revisions to the package insert (PI) and the patient package insert (PPI), incorporating safety data from the Women's Health Initiative (WHI) study.

Supplement 039 provides for the addition of a Geriatric Use Labeling subsection as a part of the "Precautions" section in the label.

We have reviewed these supplements and their corresponding amendments. These applications, as amended, are approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text.

Please submit final printed labeling (FPL) as attached to this letter which incorporates the following:

Package (professional) Insert

1. The labeling text submitted to S-036 on March 18, 2003, incorporates safety data from the WHI study, and revises the "General" subsection of the PRECAUTIONS section, "Addition of a progestin when a woman has not had a hysterectomy" to read, "There is, however, a possible risk that may be associated with the use of progestins with estrogens compared to estrogen-alone treatment. This includes a possible increased risk of breast cancer." An agreement was reached to revise this portion of the PRECAUTIONS section (refer to the January 29, 2004, telephone conversation).
2. Under the subsection "Drug/Laboratory Test Interactions" number 3, (b)(4)-----

- (b)(4)-----was corrected to corticosteroids, as agreed upon in the telephone conversation held on May 19, 2004.
3. The "Geriatric Use" subsection of the PRECAUTIONS section submitted October 2, 2003, that deletes the sentence, (b)(4)-----
(b)(4)----- as agreed upon in the telephone conversation of February 9, 2004.
 4. The "Dosage and Administration" section was revised, by deleting the last sentence, (b)(4)
(b)(4)-----
(b)(4)-----" as agreed upon in the telephone conversation held on May 19, 2004.
 5. The "Initiation of Therapy" subsection has two revisions. The first being deleting the last sentence of the first paragraph, (b)(4)-----
(b)(4)-----
(b)(4)-----" The second revision involves rewording the third paragraph to read, "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 mg applied to the skin twice weekly," as agreed upon in the telephone conversation held on May 19, 2004.

Patient Package Insert

6. The second and third paragraphs have been deleted because of redundancy of information, as agreed upon in the telephone conversation held on May 19, 2004.
7. Revise the labeling text submitted on March 18, 2003, to include the agreement reached during the January 29, 2004, telephone conversation, to add in the boxed information "an estrogen hormone" as a descriptor of Estraderm.
8. The subsection (b)(4)-----
(b)(4)-----" and was deleted. The benefits are addressed in the section entitled, "What is Estraderm used for?" This change was agreed upon in the telephone conversation held on May 19, 2004.
9. A(b)(4)-----

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-081/S-036, S-039." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

If you have any questions, call Albert Perrine, RN, BSN, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daniel A. Shames
5/28/04 11:18:57 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-081/S-036 & S-039

LABELING



Estraderm[®]

estradiol transdermal system

Continuous delivery for twice-weekly application

Rx only

Prescribing Information

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

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

CARDIOVASCULAR AND OTHER RISKS

Estrogens with and without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**). Other doses of conjugated estrogens with medroxyprogesterone, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, 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.

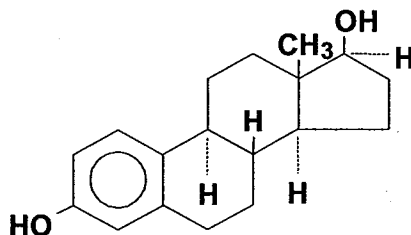
DESCRIPTION

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

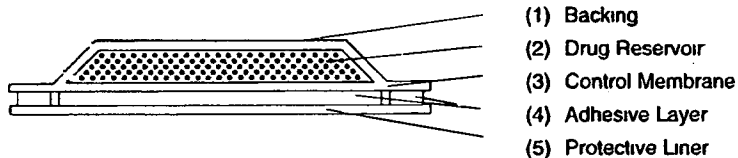
Two systems are available to provide nominal in vivo delivery of 0.05 or 0.1 mg of estradiol per day via skin of average permeability (interindividual variation in skin permeability is approximately 20%). Each corresponding system having an active surface area of 10 or 20 cm² contains 4 or 8 mg of estradiol 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 β -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 μ 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 by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. They 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.

Absorption

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.

Distribution

No specific investigation of the tissue distribution of estradiol absorbed from Estraderm in humans has been conducted. 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.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

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

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.

Special Populations

Estraderm was only investigated in postmenopausal women.

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 preparations (*Hypericum perforatum*), 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

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of the use of 0.625 mg conjugated equine estrogens (CE) per day alone and of 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". Results of the CE/MPA substudy, which included 16,608 women (average age of

63 years, range 50 to 79, 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 1 below.

Table 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI^a			
Event ^c	Relative Risk CE/MPA vs. Placebo at 5.2 Years (95% CI*)	Placebo n= 8102	CE/MPA n= 8506
		Absolute Risk per 10,000 person-years	
CHD events	1.29 (1.02-1.63)	30	37
<i>Non-fatal MI</i>	<i>1.32 (1.02-1.72)</i>	23	30
<i>CHD death</i>	<i>1.18 (0.70-1.97)</i>	6	7
Invasive breast cancer ^b	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global index ^c	1.15 (1.03-1.28)	151	170
Deep vein thrombosis ^d	2.07 (1.49-2.87)	13	26
Vertebral fractures ^d	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures ^d	0.77 (0.69-0.86)	170	131

^a adapted from JAMA, 2002: 288: 321-333

^b includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

^c 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, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

^d not included in Global index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the “global index”, absolute excess risks per 10,000 person-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the “global index”

was 19 per 10,000 person-years. There was no difference between the groups in terms of all-cause mortality (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

INDICATIONS AND USAGE

Estraderm[®] (estradiol transdermal system) is indicated in:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the 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 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

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

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Estraderm[®] (estradiol transdermal system) should not be used in patients with known hypersensitivity to its ingredients.
7. Known or suspected pregnancy. There is no indication for Estraderm in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (see **PRECAUTIONS**).

WARNINGS

See **BOXED WARNINGS**.

The use of unopposed estrogens in women who have a uterus is associated with an increased risk of endometrial cancer.

1. Cardiovascular disorders

Estrogen and estrogen/progestin therapy have been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for cardiovascular disease (e.g. hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) should be managed appropriately.

a. Coronary heart disease and stroke

In the Women's Health Initiative study (WHI), an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE alone compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 person years). The increase in risk was observed in year one and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

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

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE)

In the Women's Health Initiative study (WHI), an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the CE/MPA group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

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

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

Clinical surveillance of all women taking estrogen/progestin combinations 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 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

Estrogen and estrogen/progestin therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the CE/MPA substudy of the Women's Health Initiative study (WHI), a 26% increase of invasive breast cancer (38 vs 30 per 10,000 woman-years) after an average of 5.2 years of treatment was observed in women receiving CE/MPA compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on CE/MPA. The women reporting prior postmenopausal use of estrogen and/or estrogen with progestin had a higher relative risk for breast cancer associated with CE/MPA than those who had never used these hormones. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the WHI, no increased risk of breast cancer in CE-treated women compared to placebo was reported after an average of 5.2 years of therapy. These data are preliminary and that substudy of WHI is continuing.

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens with or without a progestin. This association was reanalyzed in original data from 51 studies that involved various doses and types of estrogens, with and without progestins. In the reanalysis, an increased risk of having breast cancer diagnosed became apparent after about 5 years of continued treatment, and subsided after treatment had been discontinued for 5 years or longer. Some later studies have suggested that postmenopausal treatment with estrogens and progestin increase the risk of breast cancer more than treatment with estrogen alone.

A postmenopausal woman without a uterus who requires estrogen should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. All postmenopausal women should receive yearly breast exams by a health care 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.

3. Gallbladder Disease

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

4. Hypercalcemia

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

5. 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 discontinued.

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 a possible 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 estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.
- 3. *Familial hyperlipoproteinemia.*** In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.
- 4. *Impaired liver function.*** Although transdermally administered estrogen therapy avoids first-pass hepatic metabolism, estrogens may be poorly metabolized in patients with impaired liver function. For patients 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. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal

range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. **Fluid retention.** Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.
7. **Hypocalcemia.** Estrogens should be used with caution in individuals with severe hypocalcemia.
8. **Ovarian cancer.** Use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with estrogen/progestin combination therapy in postmenopausal women.
9. **Exacerbation of endometriosis.** Endometriosis may be exacerbated with administration of estrogen therapy.
10. **Exacerbation of other conditions.** Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria and should be used with caution in women with these conditions.

B. Patient Information.

Physicians are advised to discuss the **Patient Information** leaflet with patients for whom they prescribe Estraderm.

C. Laboratory Tests.

Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradiol, FSH).

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 thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone

concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

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. (See **BOXED WARNINGS, CONTRAINDICATIONS, and WARNINGS.**)

F. Pregnancy.

Estrogens should not be used during pregnancy. (See **CONTRAINDICATIONS.**)

G. Nursing Mothers.

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. 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. (See **INDICATIONS and DOSAGE AND ADMINISTRATION.**)

I. Geriatric Use.

Clinical studies of Estraderm did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

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

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 estrogens:

1. **Genitourinary system.** Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.
2. **Breasts.** Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.
3. **Cardiovascular.** Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.
4. **Gastrointestinal.** Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gall bladder disease; pancreatitis.
5. **Skin.** Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.
6. **Eyes.** Retinal vascular thrombosis; steepening of corneal curvature; intolerance to contact lenses.
7. **Central nervous system.** Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy.
8. **Miscellaneous.** Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; anaphylactoid/anaphylactic reactions including urticaria and angioedema; hypocalcemia; exacerbation of asthma; increased triglycerides.

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

When estrogen is prescribed for a postmenopausal woman with a uterus, 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 limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g. 3-month to 6-month intervals) to determine whether treatment is still necessary (See **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Estraderm is currently available in two dosage forms – 0.05 mg and 0.1 mg. Patients should be started at the lowest dose.

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 (e.g., 3 weeks on drug followed by 1 week off drug).

HOW SUPPLIED

Estraderm estradiol transdermal system 0.05 mg/day – each 10 cm² system contains 4 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 SystemsNDC 0083-2310-08

Carton of 6 Patient Calendar Packs of 8 Systems.....NDC 0083-2310-62

Carton of 1 Patient Calendar Pack of 24 SystemsNDC 0083-2310-24

Estraderm estradiol transdermal system 0.1 mg/day – each 20 cm² system contains 8 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 SystemsNDC 0083-2320-08

Carton of 6 Patient Calendar Packs of 8 Systems.....NDC 0083-2320-62

Carton of 1 Patient Calendar Pack of 24 SystemsNDC 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.

REV: APRIL 2004

PATIENT INFORMATION

Estraderm®

(estradiol transdermal system)

Read this PATIENT INFORMATION before you start taking Estraderm® (estradiol transdermal system) and read all the information that you get each time you refill Estraderm. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment.

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

- Estrogens increase the chances of getting cancer of the uterus.

Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your health care provider should check any unusual vaginal bleeding to find out the cause.

- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. You and your health care 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. You and your health care provider should talk regularly about whether you still need treatment with Estraderm.

- **treat moderate to severe dryness, itching and burning in or around the vagina.**

You and your health care provider should talk regularly about whether you still need treatment with Estraderm to control these problems.

- **treat certain conditions in which a young woman's 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 health care provider about whether a different treatment or medicine without estrogens might be better for you. You and your health care provider should talk regularly about whether you should continue with Estraderm. Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your health care provider before starting them.

Who should not take Estraderm?

Do not start taking Estraderm if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.**

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

- **had a stroke or heart attack in the recent past (for example in the past year).**
- **currently have or have had blood clots.**
- **are allergic to Estraderm or any of its ingredients.**

See the end of this leaflet for a list of ingredients in Estraderm.

- **think you may be, or know that you are, pregnant.**

Tell your health care provider:

- **if you are breastfeeding.** The hormone in Estraderm can pass into your milk.
- **about all of your medical problems:** Your health care provider may need to check you more carefully if you have certain conditions such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **about all the medicines you take,** including 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 taking estrogens.

How should I take Estraderm?

Estrogens should be used only as long as needed and at the lowest possible dose that works. You and your health care provider should talk regularly (for example every 3 to 6 months) about 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 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.

What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Gallbladder disease.
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps.
- Unusual vaginal bleeding.
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision

- Vomiting

Call your health care provider right away if you get any of these warning signs, or any other unusual symptom that concerns you

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infection

Other side effects of Estraderm may be possible. If you have questions, talk to your health care provider or pharmacist.

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

- Talk with your health care provider regularly about whether you should continue taking Estraderm.
- See your health care provider right away if you get vaginal bleeding while taking Estraderm.
- Have a breast exam and mammogram (breast X-ray) every year unless your health care 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 health care provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Estraderm

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take 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 health care 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 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.

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East Hanover, New Jersey 07936

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-081/S-036 & S-039

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**Division of Reproductive and Urologic Drug Products
Project Manager Labeling Review**

Application Number: NDA 19-081/S-032, 033, 036, 039
Name of Drug: Estraderm (estradiol) transdermal system
Sponsor: Novartis Pharmaceuticals Corporation
Reviewer: Albert Perrine, Project Manager, DRUDP (HFD-580)

Material Reviewed:

S-032 Submission dated March 19, 1998 (received March 24, 1998)
 Amendment dated March 18, 2003 (received March 19, 2003)
 Amendment dated January 16, 2004 (received January 20, 2004)

S-033 Submission dated November 13, 2000 (received November 15, 2000)
 Amendment dated March 18, 2003 (received March 19, 2003)
 Amendment dated January 16, 2004 (received January 20, 2004)

S-036 Submission dated November 22, 2002 (received November 25, 2002)
 Amendment dated March 18, 2003 (received March 19, 2003)
 Amendment dated January 16, 2004 (received January 20, 2004)

S-039 Submission dated October 2, 2003 (received October 3, 2003)

Background and Summary

NDA 19-081 was approved on September 10, 1986. The last approved labeling for this NDA occurred on December 10, 1997, with the approval of supplement S-031. S-031 inserted a new pediatric use subsection that read as follows: "The safety and effectiveness in pediatric patients have not been established."

S-032, submitted as changes being effected, final printed labeling (FPL) provides for an additional revision of the ☐ ☐

Also noted was a revision of the "Contraindications" section, wherein the sponsor provides a list of conditions when estrogens should not be taken, specifically condition number 5. In the last approved package insert (PI) the sentence read, "Active thrombophlebitis or thromboembolic disorder." The sentence was revised to read,

S-033, submitted as changes being effected, final printed labeling (FPL) provides for the incorporation of safety information into the labeling as requested by the Agency in the letter dated August 16, 2000, in the "Warnings" section of the PI. Additionally this supplement corrects minor typographical errors that were also referenced in the August 2000 letter.

Current labeling was last revised September 2000, and incorporated the changes from S-032 and S-033.

S-036, submitted as "Prior Approval Labeling Supplement" specifically CFR 314.702(b), proposes addition of the Women's Health Initiative (WHI) study results.

All of the above supplements, including this one, were amended on March 18, 2003, in response to the Agency's January 3, 2003, letter requesting additional revisions and providing recommended labeling text relating to the WHI study.

Additionally, this amended supplement provides for revisions of the "Contraindications" section. The sponsor wishes to modify the Agency suggested wording for

The submission was the March 18, 2003, amendment to S-036 based on our January 3, 2003 letter to the sponsor, See S-036.

S-039, submitted as "Prior Approval Labeling Supplement" specifically CFR 201.57(f)(10)(ii)(A), provided for the inclusion of a "Geriatric Use" subsection within the "Precautions" section of the PI.

Review

The labeling submitted in 19-081/S-032, 033, 036, and 039 were compared to the following:

- The approved PI submitted January 27, 1997, to supplement 031 (approved December 10, 1997).
- The requests made in the Agency's August 16, 2000, letter requesting that safety information be incorporated into the label for Estraderm as a CBE.

- The approvable letter for supplement S-033, dated September 19, 2002, wherein the Agency request that the sponsor address the published unfavorable findings from the July 9, 2002, National Heart Lung and Blood Institute's (NHLBI) WHI study of the benefit to risk profile of Prempro for primary prevention of coronary heart disease.
- The requests made in the January 3, 2003, letter with attached recommended labeling text.
- The decisions reached in the October 30, 2003, team meeting regarding the requested boxed warning, recommended labeling text, indications, and currently approved labeling text.

The revisions to the labeling, package insert and patient package insert are extensive. Each section of the labeling is addressed in the following combined review of S-032, 033, 036, and 039:

Package (professional) Insert Review:

1. Boxed Warning: Revised as requested with one addition. Novartis qualifies the last sentence in first paragraph by stating that, "There is **currently** no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose." The revision is acceptable as the content remains consistent with the recommended labeling text. Added text



2. DESCRIPTION: Minor chemistry revisions made to product layer descriptions in this section.

Below, the revisions will be in bold print:

- (a) the backing is a transparent polyester/**ethylene vinyl acetate copolymer** film
- (b) the drug reservoir of estradiol USP and alcohol USP gelled with hydroxypropyl cellulose NF
- (c) the control membrane description is unchanged
- (d) the adhesive layer is a formulation of light mineral oil NF and polyisobutylene
- (e) the protective layer of siliconized **polyester** film is attached to the adhesive surface and must be removed before the system can be used. The sponsor deleted



The revisions found in this section were confirmed (S-035, approved March 14, 2002) and are acceptable.

3. CLINICAL PHARMACOLOGY:

- (a) The introductory paragraphs are identical to the recommended WHI language and are acceptable.
- (b) Pharmacokinetics: This section has been revised to be identical in content to the

recommended labeling text. Metabolism and bioavailability language from the last approved PI was retained. With the revisions to this section, the sponsor clearly articulates the action of this drug with a transdermal route of administration. This change is acceptable.

- (c) Absorption: This heading was added and the language used was taken from currently approved language from the "Pharmacokinetics" sections and placed under this new heading. Because the language is currently approved, this revision is acceptable.
- (d) Distribution: The opening sentence is new, but offers clarifying language. The remaining sentences in this section are consistent with approved WHI language. This section is acceptable.
- (e) Metabolism: The sponsor has agreed to delete last sentence in this section as a result of the January 15, 2004, teleconference. The sponsor has submitted an amendment dated January 16, 2004, to that effect. The currently approved labeling text has been retained and is acceptable.
- (f) Excretion: The currently approved language is retained. The sponsor also incorporates approved language from the "Clinical Pharmacology" section. The language is found to be acceptable.
- (g) Special Populations: Added a new section "Special Populations" because the sponsor's study population only consisted of postmenopausal women. This is acceptable.
- (h) Drug Interaction: As a result of the January 15, 2004, teleconference, referenced in the January 16, 2004, amendment, the sponsor will delete the last sentence in this section. This is acceptable.

4. INDICATIONS AND USAGE: Estraderm is approved for the treatment of the following symptoms associated with the menopause:

- (a) Moderate to severe vasomotor symptoms
- (b) Vulvar and vaginal atrophy
- (c) Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure
- (d) Prevention of postmenopausal osteoporosis

This section has been revised incorporating the changes recommended in the January 3, 2003. It is acceptable

5. CONTRAINDICATIONS: The revisions of the section are identical to those requested in the recommended WHI labeling.

6. WARNINGS: The sponsor has revised this section and the language is very close to the requested recommended WHI language. Under a. Coronary Heart Disease, delete reference to **C** **3**. Under section 2 (b) "Breast Cancer" in the second and third sentences the sponsor added the following bolded words: "All postmenopausal women should receive yearly breast exams by a health care 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. These additions to the recommended language will provide clarity

to the consumer. This is acceptable.

7. PRECAUTIONS: The sponsor has revised this section according to the requested recommended WHI language.

General:

- (a) The subheading [] has been changed to, "Addition of a progestin when a woman has not had a hysterectomy." This information was added in accordance with the WHI language. It is recommended that the sponsor revise this section to: "There [] that may be associated with the use of progestins with estrogens compared to estrogen-alone [] This includes a possible increased risk of breast cancer." This language is currently in use for NDA 20-907, Activella® and is appropriate. The impair[] of glucose tolerance test is addressed in section D, Drug/Laboratory Test Interactions and should be deleted from the General subsection. The sponsor agreed to these recommendations in the January 30, 2004, teleconference.
- (b) The subheading "Cardiovascular []" has been deleted and that information can be found in the Boxed Warning, the "Clinical Studies" section, and the "Warnings" section. This is acceptable
- (c) Elevated blood pressure: The wording is identical to the recommended WHI language. This is acceptable.
- (d) Familial hyperlipoproteinemia: The wording is identical to the requested recommended WHI language. This is acceptable.
- (e) Impaired liver function: The first part of the first sentence, "Although transdermally administered estrogen therapy avoids first-pass metabolism" is taken from the Pharmacokinetic section of the WHI recommended language. The remaining wording is identical to the recommended WHI language for this section. This is acceptable. The sponsor should add "cholestatic" prior to the word jaundice.
- (f) Hypothyroidism: This wording in this section is identical to the requested recommended WHI language.
- (g) Fluid retention: The wording is identical to recommended WHI language except for the inclusion of other condition that could be effected by fluid retention: asthma, epilepsy, and migraine headaches. These condition are taken from the patient information page, under "Side Effects." Also included in "Exacerbation of other condition" section. This is acceptable.
- (h) Hypocalcemia: Information was added based on recommended WHI language. This is acceptable.
- (i) Ovarian cancer: Information was added based on recommended WHI language. This is acceptable.
- (j) Exacerbation of endometriosis: Information added based on recommended WHI language. This is acceptable.
- (k) Exacerbations of other conditions: Information added based on recommended WHI language. This is acceptable.

8. Patient Information: Wording revised to be consistent with recommended WHI language. This is acceptable.
9. Laboratory Tests: This section was revised to be consistent with recommended WHI language. This is acceptable.
10. Drug/Laboratory Test Interactions: The opening sentence, []
[]
[] have been deleted as recommended by FDA. Other than these two deletions, the currently approved labeling text has been retained. This is acceptable.
11. Carcinogenesis, Mutagenesis, Impairment of Fertility: The following two bolded items, as recommended were added to this section: "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. (See **BOXED WARNINGS, CONTRAINDICATIONS, AND WARNINGS.**) Other than the bolded items the currently approved language was retained. This is acceptable.
12. Pregnancy: The heading was revised from [] to "Pregnancy."
See [] has been deleted. Both changes are consistent with the recommended labeling text. Other than these two changes, the currently approved language has been retained. This is acceptable.
13. Nursing Mothers: This section has been revised to reflect the requested recommended WHI language. This is acceptable.
14. Pediatric Use: This section has been revised to add the standard labeling text for products indicated for hypogonadism. This is acceptable.
15. Geriatric Use: With S-039, the sponsor has added a "Geriatric Use" subsection. The sponsor agreed to delete the second sentence. This is acceptable.
16. Adverse Reactions: This section has been revised to be consistent with the recommended labeling text.
 - (a) Genitourinary: With the addition of the following conditions this section has been revised to reflect the requested recommended WHI Language: **vaginitis, changes in cervical ectropion, ovarian cancer, endometrial hyperplasia, and endometrial cancer.** This is acceptable.
 - (b) Breasts: With the addition of the following conditions, signs, and symptoms, this section has been revised to reflect the requested recommended WHI language: **pain, nipple discharge, galactorrhea, fibrocystic breast changes, and breast cancer.** This is acceptable.

- (c) Cardiovascular: Information added based on recommended WHI language. This is acceptable.
 - (d) Gastrointestinal: The following conditions in bold type have been added as recommended: Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, **increased incidence of gall bladder disease, and pancreatitis**. This is acceptable.
 - (e) Skin: The sponsor has the following two conditions to reflect the requested recommended WHI Language: pruritus and rash. This revision is acceptable.
 - (f) Eyes: The condition retinal vascular thrombosis has been added to this section and is consistent with the recommended labeling text. This is acceptable.
 - (g) Central Nervous System: The following conditions have been added to this section: mood disturbances, irritability, and exacerbation of epilepsy. This revision is acceptable and is consistent with the recommended labeling text.
 - (h) Miscellaneous: The following conditions have been added: anaphylactoid/anaphylactic reactions including urticaria and angioedema, hypocalcemia, exacerbation of asthma and increased triglycerides. This is acceptable and is consistent with the recommended labeling text.
17. Overdosage: The heading has been changed from [] Overdosage" to "Overdosage." The current approved wording has been retained. This minor change is acceptable and consistent with 21CFR201.57(j).
18. Dosage and Administration: The sponsor has formatted this section with a subheading entitled "Initiation of Therapy." This section has editorial revisions regarding initiation of therapy for conditions that this product is approved to treat. This is acceptable.
19. How Supplied: This section is unchanged and is acceptable.

Patient Package Insert:

The patient package insert (PPI) submitted in S-032, 033 and S-036 were all amended March 18, 2003 and compared to the approved PPI submitted January 27, 1997 to supplement S-031 (approved December 10, 1997) and to the recommended labeling changes attached to the January 3, 2003 letter. The following changes were noted:

- 1. Instructions for the patient to read the leaflet prior to taking Estraderm is added based on recommended labeling text. This is acceptable. The sponsor should delete the new second and third paragraphs, because this is redundant information found within the labeling.
- 2. Boxed Warning revised to reflect currently recommended labeling text. One discrepancy is that the revised Boxed Warning omitted "(an estrogen hormone)?" This omission is not acceptable and should be included. Other than this oversight the wording is identical to the recommended labeling text. Once "(an estrogen hormone)"

is added this will be acceptable. The sponsor agreed to add this phrase during our January 30, 2004, teleconference.

3. What is Estraderm?: The currently approved wording is retained. This is acceptable.
4. What is Estraderm used for?: The currently approved subtitles and language are retained, with the addition of the following statement, "treat certain conditions in which a young women's ovaries do not produce enough estrogens naturally." This is acceptable as it is consistent with the approved indication for Estraderm for treatment of hypogonadism.
5. Who should not take Estraderm?: This section has been revised and is identical to the recommended labeling text. This is acceptable.
6. Tell your health care provider: This section has been revised and is identical to the recommended labeling text. This is acceptable.
7. How should I take Estraderm?: The language in this section is consistent with the recommended labeling text.
8. Instructions on how, where, and when to apply Estraderm are unchanged and retained from the currently approved PPI. This is acceptable. []
[] []
[] []
9. The subheading, "Benefits of treatment with Estraderm" and the subsequent language are both unchanged and retained from the currently approved PPI. This is acceptable.
10. What are the possible side effects of estrogens?: This section is identical to the recommended labeling text except for the statement listed under the subheading "Other [] side effects." The difference is editorial in nature. The context is the same. This is acceptable.
11. General information about safe and effective use of Estraderm: This section has been revised and is identical to the recommended labeling text. This is acceptable.
12. What are the ingredients in Estraderm?: This section has been revised and the language used is identical to the recommended labeling text. The ingredients are consistent with those listed in the "Description" section of the PI. This is acceptable.
13. All [] [] should be deleted, because the [] [] statements have been deleted.

Conclusion:

Supplements 032, and 033 should be Acknowledged and Retained because these supplements are superceded by S-036. This letter was sent to the sponsor March 1, 2004.

S-036 should be approved with the Agency recommended additions and revisions.

Supplement 039 dated October 2, 2003, has been Acknowledged. S-039 should be approved. The final printed labeling for S-036 and S-039 must include all revisions and agreements covered by both supplements and should be in agreement with the labeling attached to the approval letter.



Estraderm[®]

estradiol transdermal system

Continuous delivery for twice-weekly application

Rx only

Prescribing Information

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

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

CARDIOVASCULAR AND OTHER RISKS

Estrogens with and without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**). Other doses of conjugated estrogens with medroxyprogesterone, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, 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

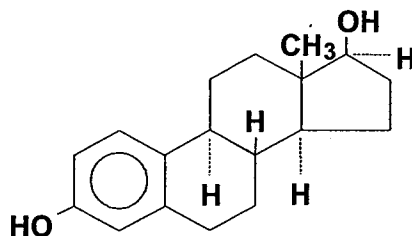
Estraderm, estradiol transdermal system, is designed to release estradiol through a rate-limiting membrane continuously upon application to intact skin.

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

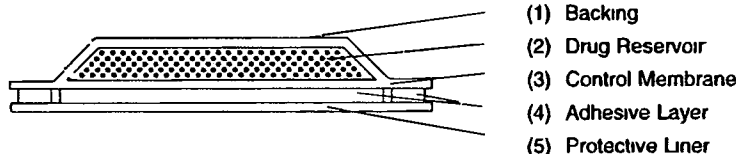
permeability is approximately 20%). Each corresponding system having an active surface area of 10 or 20 cm² contains 4 or 8 mg of estradiol USP and 0.3 or 0.6 mL of alcohol USP, respectively. The composition of the systems per unit area is identical.

Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17 β -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 μ 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 by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. They 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.

Absorption

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.

Distribution

No specific investigation of the tissue distribution of estradiol absorbed from Estraderm in humans has been conducted. 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.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

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

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.

Special Populations

Estraderm was only investigated in postmenopausal women.

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 preparations (*Hypericum perforatum*), 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

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of the use of 0.625 mg conjugated equine estrogens (CE) per day alone and of 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79, 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 1 below.

Table 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI^a			
Event ^c	Relative Risk CE/MPA vs. Placebo at 5.2 Years (95% CI*)	Placebo n= 8102	CE/MPA n= 8506
		Absolute Risk per 10,000 person-years	
CHD events	1.29 (1.02-1.63)	30	37
<i>Non-fatal MI</i>	<i>1.32 (1.02-1.72)</i>	23	30
<i>CHD death</i>	<i>1.18 (0.70-1.97)</i>	6	7
Invasive breast cancer ^b	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global index ^c	1.15 (1.03-1.28)	151	170
Deep vein thrombosis ^d	2.07 (1.49-2.87)	13	26
Vertebral fractures ^d	0.66 (0.44-0.98)	15	9

Other osteoporotic fractures ^d	0.77 (0.69-0.86)	170	131
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^a adapted from JAMA, 2002: 288: 321-333

^b includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

^c 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, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

^d not included in Global index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the “global index”, absolute excess risks per 10,000 person-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the “global index” was 19 per 10,000 person-years. There was no difference between the groups in terms of all-cause mortality (See **BOXED WARNINGS, WARNINGS, and PRECAUTIONS.**)

INDICATIONS AND USAGE

Estraderm[®] (estradiol transdermal system) is indicated in:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the 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 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

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

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Estraderm® (estradiol transdermal system) should not be used in patients with known hypersensitivity to its ingredients.
7. Known or suspected pregnancy. There is no indication for Estraderm in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (see **PRECAUTIONS**).

WARNINGS

See **BOXED WARNINGS**.

The use of unopposed estrogens in women who have a uterus is associated with an increased risk of endometrial cancer.

1. Cardiovascular disorders

Estrogen and estrogen/progestin therapy have been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for cardiovascular disease (e.g. hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) should be managed appropriately.

a. Coronary heart disease and stroke

In the Women's Health Initiative study (WHI), an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE alone compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 person years). The increase in risk was observed in year one and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

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

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE)

In the Women's Health Initiative study (WHI), an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the CE/MPA group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

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

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears associated with prolonged use with

increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations 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 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

Estrogen and estrogen/progestin therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the CE/MPA substudy of the Women's Health Initiative study (WHI), a 26% increase of invasive breast cancer (38 vs 30 per 10,000 woman-years) after an average of 5.2 years of treatment was observed in women receiving CE/MPA compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on CE/MPA. The women reporting prior postmenopausal use of estrogen and/or estrogen with progestin had a higher relative risk for breast cancer associated with CE/MPA than those who had never used these hormones. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the WHI, no increased risk of breast cancer in CE-treated women compared to placebo was reported after an average of 5.2 years of therapy. These data are preliminary and that substudy of WHI is continuing.

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens with or without a progestin. This association was reanalyzed in original data from 51 studies that involved various doses and types of estrogens, with and without progestins. In the reanalysis, an increased risk of having breast cancer diagnosed became apparent after about 5 years of continued treatment, and subsided after treatment had been discontinued for 5 years or longer. Some later studies have suggested that postmenopausal treatment with estrogens and progestin increase the risk of breast cancer more than treatment with estrogen alone.

A postmenopausal woman without a uterus who requires estrogen should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. All postmenopausal women should receive yearly breast exams by a health care 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.

3. Gallbladder Disease

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

4. Hypercalcemia

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

5. 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 discontinued.

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 a possible 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 estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.
3. **Familial hyperlipoproteinemia.** In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.
4. **Impaired liver function.** Although transdermally administered estrogen therapy avoids first-pass hepatic metabolism, estrogens may be poorly metabolized in patients with impaired liver function. For patients 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. Patients with normal thyroid function can compensate for

the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. **Fluid retention.** Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.
7. **Hypocalcemia.** Estrogens should be used with caution in individuals with severe hypocalcemia.
8. **Ovarian cancer.** Use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with estrogen/progestin combination therapy in postmenopausal women.
9. **Exacerbation of endometriosis.** Endometriosis may be exacerbated with administration of estrogen therapy.
10. **Exacerbation of other conditions.** Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria and should be used with caution in women with these conditions.

B. Patient Information.

Physicians are advised to discuss the **Patient Information** leaflet with patients for whom they prescribe Estraderm.

C. Laboratory Tests.

Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradiol, FSH).

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 thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

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. (See **BOXED WARNINGS, CONTRAINDICATIONS, and WARNINGS.**)

F. Pregnancy.

Estrogens should not be used during pregnancy. (See **CONTRAINDICATIONS.**)

G. Nursing Mothers.

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. 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. (See INDICATIONS and DOSAGE AND ADMINISTRATION.)

I. Geriatric Use.

Clinical studies of Estraderm did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

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

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 estrogens:

1. **Genitourinary system.** Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.
2. **Breasts.** Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.
3. **Cardiovascular.** Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.
4. **Gastrointestinal.** Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gall bladder disease; pancreatitis.

5. **Skin.** Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.
6. **Eyes.** Retinal vascular thrombosis; steepening of corneal curvature; intolerance to contact lenses.
7. **Central nervous system.** Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy.
8. **Miscellaneous.** Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; anaphylactoid/anaphylactic reactions including urticaria and angioedema; hypocalcemia; exacerbation of asthma; increased triglycerides.

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

When estrogen is prescribed for a postmenopausal woman with a uterus, 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 limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g. 3-month to 6-month intervals) to determine whether treatment is still necessary (See **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be

undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Estraderm is currently available in two dosage forms – 0.05 mg and 0.1 mg. Patients should be started at the lowest dose.

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 (e.g., 3 weeks on drug followed by 1 week off drug).

HOW SUPPLIED

Estraderm estradiol transdermal system 0.05 mg/day – each 10 cm² 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 SystemsNDC 0083-2310-24

Estraderm estradiol transdermal system 0.1 mg/day – each 20 cm² 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 SystemsNDC 0083-2320-

*See DESCRIPTION.

Do not store above 30°C (86°F).

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

REV: APRIL 2004

PATIENT INFORMATION

Estraderm® (estradiol transdermal system)

Read this PATIENT INFORMATION before you start taking Estraderm® (estradiol transdermal system) and read all the information that you get each time you refill Estraderm. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment.

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

- Estrogens increase the chances of getting cancer of the uterus.

Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your health care provider should check any unusual vaginal bleeding to find out the cause.

- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. You and your health care 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. You and your health care provider should talk regularly about whether you still need treatment with Estraderm.

- **treat moderate to severe dryness, itching and burning in or around the vagina.**

You and your health care provider should talk regularly about whether you still need treatment with Estraderm to control these problems.

- **treat certain conditions in which a young woman's 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 health care provider about whether a different treatment or medicine without estrogens might be better for you. You and your health care provider should talk regularly about whether you should continue with Estraderm. Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your health care provider before starting them.

Who should not take Estraderm?

Do not start taking Estraderm if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.**

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

- **had a stroke or heart attack in the recent past (for example in the past year).**
- **currently have or have had blood clots.**
- **are allergic to Estraderm or any of its ingredients.**

See the end of this leaflet for a list of ingredients in Estraderm.

- **think you may be, or know that you are, pregnant.**

Tell your health care provider:

- **if you are breastfeeding.** The hormone in Estraderm can pass into your milk.
- **about all of your medical problems:** Your health care provider may need to check you more carefully if you have certain conditions such as asthma (wheezing),

epilepsy (seizures), migraine, endometriosis, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **about all the medicines you take**, including 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 taking estrogens.

How should I take Estraderm?

Estrogens should be used only as long as needed and at the lowest possible dose that works. You and your health care provider should talk regularly (for example every 3 to 6 months) about 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 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.

What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Gallbladder disease.
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps.
- Unusual vaginal bleeding.
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath

- Pains in your legs
- Changes in vision
- Vomiting

Call your health care provider right away if you get any of these warning signs, or any other unusual symptom that concerns you

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infection

Other side effects of Estraderm may be possible. If you have questions, talk to your health care provider or pharmacist.

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

- Talk with your health care provider regularly about whether you should continue taking Estraderm.
- See your health care provider right away if you get vaginal bleeding while taking Estraderm.

- Have a breast exam and mammogram (breast X-ray) every year unless your health care 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 health care provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Estraderm

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take 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 health care 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 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.

NDA 19-081/S-032, 033, 036, 039

Page 31



Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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/s/

Albert Perrine
5/25/04 11:52:00 AM
CSO

Margaret Kober
5/25/04 01:19:21 PM
CSO

**Division of Reproductive and Urologic Drug Products
Industry Teleconference Meeting Minutes**

Sponsor: Novartis Pharmaceuticals Corporation
NDA: 19-081/S-036
Drug: Estraderm® (estradiol transdermal system)
Date: 30 January 2004
Location: 18B-09 (Albert's office)
Time: 10:22 am – 10:40 am
Type: Guidance

FDA Attendee:

Albert Perrine, RN, BSN, Regulatory Project Manager, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)

Novartis Attendee:

Kevin Carl, PharmD., Assistant Director, Drug Regulatory Affairs

Background:

This teleconference was requested by the Division to discuss the issues concerning the most recent labeling submission for NDA 19-081/S-036, in reference to the Women's Health Initiative (WHI) study.

Discussion:

1. DRUDP requested that the sponsor again revise the "PRECAUTIONS" section incorporating the most recently recommended labeling text concerning lipoprotein metabolism as found in Vivelle (an estradiol transdermal also sponsored by Novartis), and deleting the possible risk of, "[] glucose tolerance" from this section since it is addressed in the "Drug/Laboratory Test Interactions" section. The language was discussed with the sponsor in detail.

Novartis: Dr. Carl is in agreement with the proposed revisions to this section.

2. After further review of the Patient Package Information (PPI) it was discovered that in the Boxed Section, "What is the most important information I should know about Estraderm (an estrogen hormone)?" the sponsor omitted "(an estrogen hormone)."

Novartis: Dr. Carl apologized for the oversight and stated that he is in agreement with the proposed revision to this section.

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On Original

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/s/

Albert Perrine
3/26/04 08:03:42 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-081/S-039

Novartis Pharmaceuticals Corporation
Attention: Kevin M. Carl, Pharm.D.
Assistant Director
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Carl:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act or the following:

Name of Drug Product: Estraderm® (estradiol transdermal system)

NDA Number: 19-081

Supplement number: S-039

Date of supplement: October 2, 2003

Date of receipt: October 3, 2003

This supplemental application, submitted as "Prior Approval Labeling Supplement" proposes the addition of a **Geriatric Use** subsection, as a part of the **PRECAUTIONS** section of the labeling.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call Albert Perrine, RN, BSN, Regulatory Project Manager, at (301) 827-7511.

Sincerely,

{See appended electronic signature page}

Kassandra Sherrod, R.Ph.
Regulatory Project Manager
Division of Reproductive Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Kassandra C. Sherrod
11/12/03 02:41:56 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-081/S-032, S-033, S-036

Novartis Pharmaceuticals
Attention: Sheryl LeRoy
Associate Director
Global Regulatory CMC
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. LeRoy:

Please refer to your supplemental new drug applications dated March 19, 1998, received March 24, 1998 (S-032), November 13, 2000, received November 15, 2000 (S-033) and November 22, 2002 received November 25, 2002 (S-036), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estraderm (estradiol).

We also refer to our October 30, 2002, letter informing you that we planned to send you our suggested labeling changes based on the results of the Women's Health Initiative (WHI) trial by early January 2003. The information from the WHI trial about estrogens and progestins has significant public health implications for postmenopausal women. We believe all health care providers who prescribe estrogen- and progestin-containing drug products for postmenopausal women and all postmenopausal women who are prescribed these products need to know about the new risk information so that they can make appropriate health decisions. We are requesting all manufacturers of estrogen- and progestin-containing products for use by postmenopausal women to update the labeling for their products to include this information.

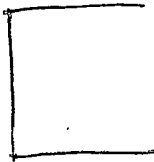
Please submit amendments to these supplements, within 60 days, providing draft labeling for Estraderm that incorporates revisions to the labeling sections indicated in this letter and that are appropriate to the approved indications for Estraderm.

Background

On July 5, 2002, the Food and Drug Administration (FDA) was informed by the National Heart, Lung, and Blood Institute's (NHLBI) Women's Health Initiative (WHI) program that they stopped the combination estrogen plus progestin trial in postmenopausal women with intact uteri because of an increased risk for invasive breast cancer. The NHLBI reported a 26% increase in breast cancer rates, 29% increase in heart attacks, 41% increase in strokes, and 100% increase in

venous thromboembolism rates, including pulmonary embolism for women taking 0.625mg/day of conjugated equine estrogens plus 2.5mg/day of medroxyprogesterone acetate compared to placebo.

On August 13, 2002, FDA released a public statement on the results of the WHI trial. In this statement, FDA advised women taking conjugated equine estrogens plus medroxyprogesterone or other combination estrogen/progestin therapy to consult with their health care providers about the relevance of this new information to their treatment.



On October 23 and 24, 2002, the National Institutes of Health held a public forum to discuss the WHI findings. Representatives from FDA participated in this public discussion. Based on information from this meeting, other information, and our preliminary analysis of the WHI data, we have determined that the labeling for estrogen and progestin drug products should be revised to provide for safe and effective use of these drugs for their labeled indications.

Requested Labeling Changes

The risk information from the WHI is critical to an individual's decision about estrogen and progestin use and should be highlighted accordingly. The recommended labeling changes provide this new information on risk, highlighting particular risk data and stating what is known and not known about the risks. There are also revisions to encourage use of estrogens and progestins in the appropriate population of postmenopausal women for whom benefits may exceed risks and in a manner to minimize risks. In addition, the recommended changes include updated information not directly related to the WHI findings.

The revisions are presented in greater detail in the attachment enclosed with this letter. If you have evidence from controlled clinical trials that demonstrates a different risk profile than that described in the recommended labeling revision, please submit these data along with your proposed revised labeling. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the proposed changes.

Your revised labeling should eliminate references to "postmenopausal hormone replacement therapy," "postmenopausal hormone therapy," and similar phrases. Menopause induces many symptoms. Estrogens in general, however, are approved to treat only specific symptoms that occur with menopause: moderate to severe vasomotor symptoms (VMS) and vulvar and vaginal atrophy (VVA). It is misleading to broadly imply that estrogens are indicated for any woman who has achieved menopause. Furthermore, the approved uses of estrogen products for the treatment of VMS and VVA are not "hormone replacement" indications, but specific symptomatic relief indications. Therefore, use of "replacement" is inappropriate.

1. **CLINICAL PHARMACOLOGY:** Revise this section as necessary to provide the most current information about the pharmacokinetics of estradiol, e.g., specific information is currently available from in vitro and in vivo studies demonstrating the metabolism of estrogen.
2. **CLINICAL STUDIES:** Add information about the WHI study.
3. **INDICATIONS AND USAGE:** Revise this section according to information in the attachment for the currently approved indications for Estraderm.
4. **CONTRAINDICATIONS:** Revise this section to reflect the updated information from the WHI study. Also, known or suspected pregnancy remains a contraindication. However, current human exposure data for estrogens and progestins in oral contraceptives suggest little or no increased risk to the fetus.
5. **WARNINGS:** The information from the WHI is significant to the benefit-risk evaluations that physicians need to make when prescribing Estraderm and to the decision women make regarding whether or not to take this drug. Therefore, substantial revisions to the warnings included in the labeling are needed. The risks for myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women should be emphasized. ☒ ☐ ☐
6. **PRECAUTIONS:** Add the information relating to effects of estrogen/progestin therapy on ovarian cancer. ☒ ☐ ☐
7. **ADVERSE REACTIONS:** Revise to include the recommended information. Reorder information in this section to give greater prominence to cardiovascular events.
8. **DOSAGE AND ADMINISTRATION:** Appropriate changes are necessary to be consistent with the risks associated with estrogens used with or without a progestin.
9. **PATIENT INFORMATION:** Update the patient information leaflet to be consistent with the revisions to the professional labeling.

If you have any questions, call Kassandra Sherrod, R.Ph., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

18 page(s) of draft
labeling has been
removed from this
portion of the review.

1/3/03 Correspondence

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/s/

Donna Griebel

1/3/03 03:06:21 PM

Signed for Division Director, Dr. Daniel Shames, MD