ESTRADIOL TRANSDERMAL SYSTEM- estradiol patch
Praxis, LLC

Estradiol Transdermal System

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

the Estradiol Transdermal System is not indicated for use in pregnancy. There are no data with the use of the Estradiol Transdermal System in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives (estrogens and progestins) before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

Estrogens are present in human milk and can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for the Estradiol Transdermal System and any potential adverse effects on the breastfed child from the Estradiol Transdermal System or from the underlying maternal condition.

8.4 Pediatric Use

In general, the Estradiol Transdermal System is not indicated for use in pediatric patients. Clinical studies have not been conducted in the pediatric population.

If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone metabolism and effects on epiphyseal centers is recommended during estrogen administration.

8.5 Geriatric Use

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

The Women’s Health Initiative Studies

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there

was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.3)]* .

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.3)]* .

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions (5.3), and Clinical Studies (14.4)]* .

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [8]*[see Warnings and Precautions (5.3), and Clinical Studies (14.4)]* .

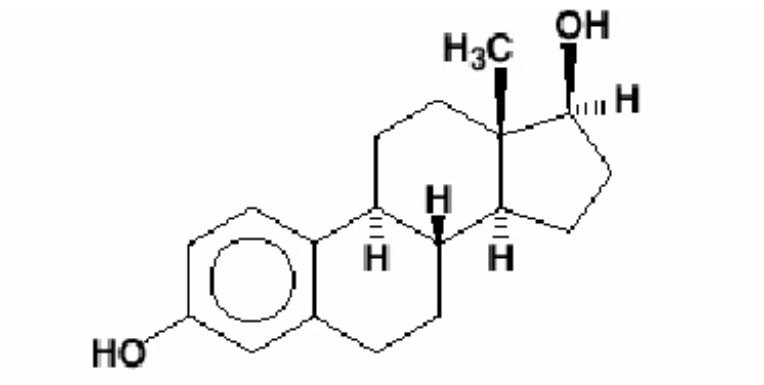
10 OVERDOSAGE

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

11 DESCRIPTION

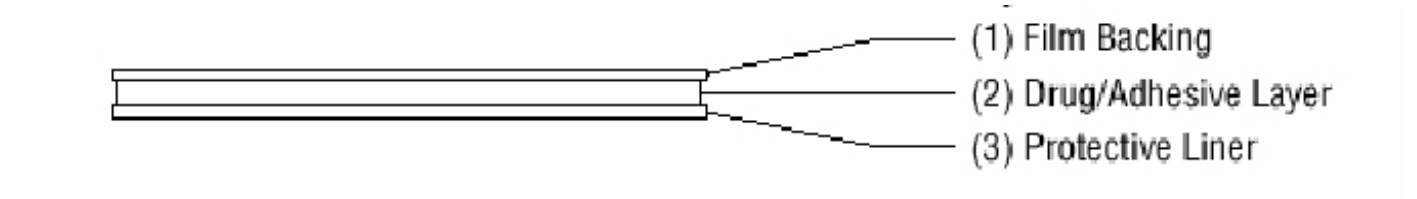
The Estradiol Transdermal System (estradiol transdermal system), is designed to release estradiol continuously upon application to intact skin. Six (6.5, 9.375, 12.5, 15, 18.75 and 25 cm^2) systems are available to provide nominal *in vivo*delivery of 0.025, 0.0375, 0.05, 0.06, 0.075 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 9.375, 12.5, 15, 18.75 or 25 cm^2, and contains 2, 2.85, 3.8, 4.55, 5.7 or 7.6 mg of estradiol 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, 17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$and molecular weight of 272.38. The structural formula is:



The Estradiol Transdermal System transdermal system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are:

1. A translucent polyethylene film.
2. An acrylate adhesive matrix containing estradiol USP.
3. A protective liner of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the system can be used.



The active component of the transdermal system is estradiol. The remaining components of the transdermal system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, which is secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

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

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

Generally, a serum estrogen concentration does not predict an individual woman’s therapeutic response to the Estradiol Transdermal System nor her risk for adverse outcomes. Likewise, exposure comparisons across different estrogen products to infer efficacy or safety for the individual woman may not be valid.

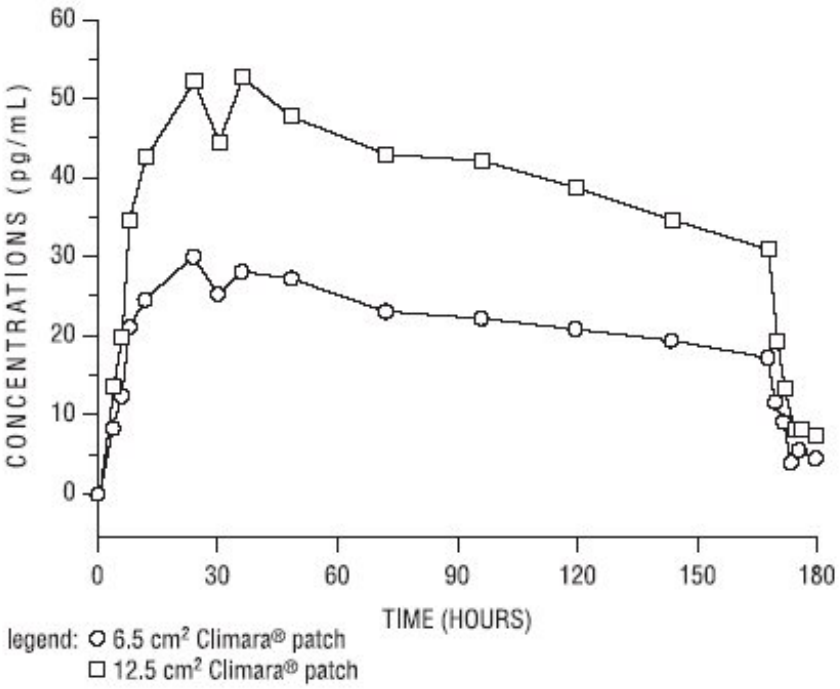
12.3 Pharmacokinetics

Absorption

Transdermal administration of the Estradiol Transdermal System produces mean serum concentrations of estradiol comparable to those produced by premenopausal women in the early follicular phase of the ovulatory cycle. The pharmacokinetics of estradiol following application of the Estradiol Transdermal System transdermal system were investigated in 197 healthy postmenopausal women in six studies. In five of the studies, the Estradiol Transdermal System transdermal system was applied to the abdomen, and in a sixth study, application to the buttocks and abdomen were compared.

The Estradiol Transdermal System transdermal delivery system continuously releases estradiol which is transported across intact skin leading to sustained circulating levels of estradiol during a 7-day treatment period. The systemic availability of estradiol after transdermal administration is about 20 times higher than that after oral administration. This difference is due to the absence of first pass metabolism when estradiol is given by the transdermal route.

In a bioavailability study, the Estradiol Transdermal System 6.5 cm ^{2}was studied with the Estradiol Transdermal System 12.5 cm ^{2}as reference. The mean estradiol levels in serum from the two sizes are shown in Figure 1.



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

Dose proportionality was also demonstrated for the Estradiol Transdermal System (12.5 cm ^{2}and 25 cm ^{2}) in a 1-week study conducted in 54 postmenopausal women. The mean steady state levels (C_{avg}) of the estradiol during the application of the Estradiol

Transdermal System 25 cm ^{2}and 12.5 cm ^{2}on the abdomen were about 80 and 40 pg/mL, respectively.

In a 3-week multiple application study in 24 postmenopausal women, the 25 cm ^{2}Estradiol Transdermal System produced average peak estradiol concentrations (C_{max}) of approximately 100 pg/mL. Trough values at the end of each wear interval (C_{min}) were approximately 35 pg/mL. Nearly identical serum curves were seen each week, indicating little or no accumulation of estradiol in the body. Serum estrone peak and trough levels were 60 and 40 pg/mL, respectively.

In a single dose, randomized, crossover study conducted to compare the effect of site of application, 38 postmenopausal women wore a single Estradiol Transdermal System 25 cm ^{2}transdermal system for 1 week on the abdomen and buttocks. The estradiol serum concentration profiles are shown in Figure 2. Values of $C_{max}$and C_{avg}were, respectively, 25 percent and 17 percent higher with the buttock application than with the abdomen application.

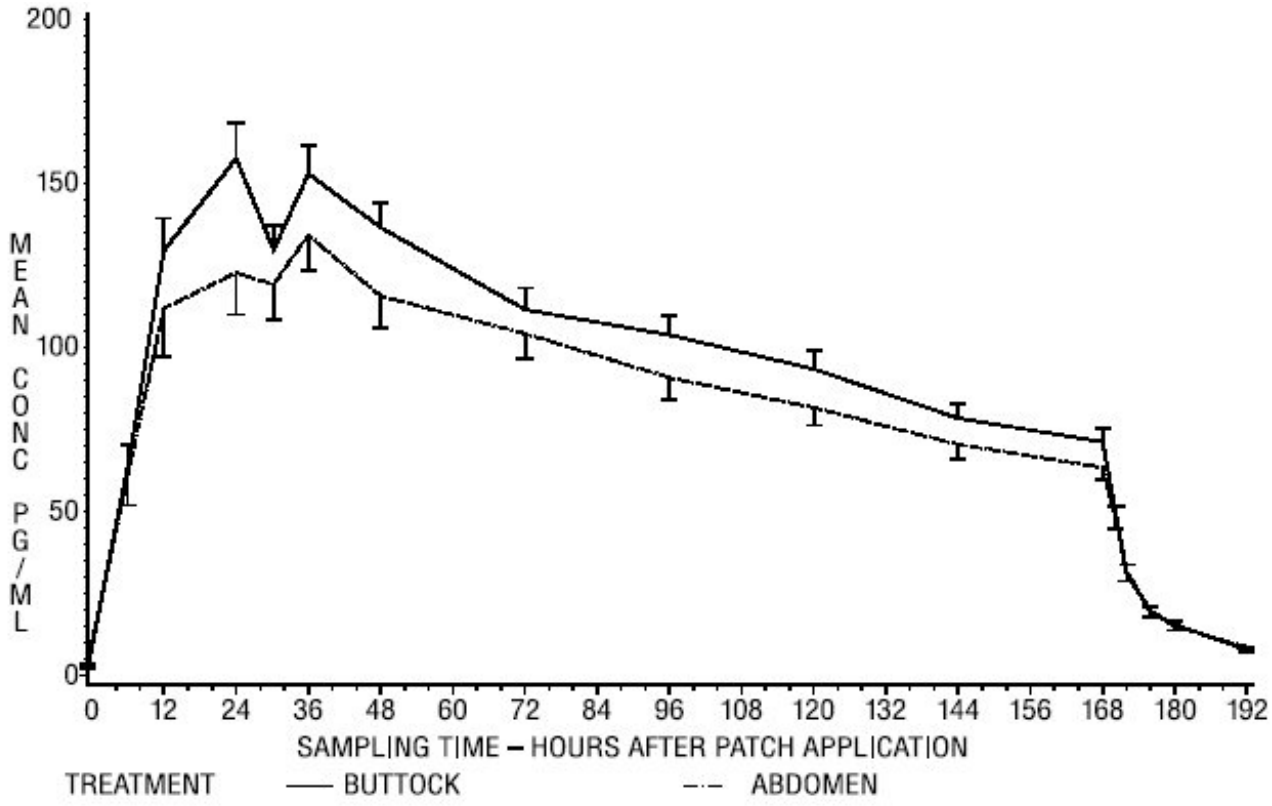


Table 2 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of the Estradiol Transdermal System transdermal system.

Table 2: Pharmacokinetic Summary (Mean Estradiol Values)

Estradiol Transdermal System Delivery Rate	Surface Area (cm ^{2})	Application Site	No. of Subjects	Dosing	C_{max} (pg/mL)	C_{min} (pg/mL)	C_{avg} (pg/mL)

0.025	6.5	Abdomen	24	Single	32	17	22
0.05	12.5	Abdomen	102	Single	71	29	41
0.1	25	Abdomen	139	Single	147	60	87
0.1	25	Buttock	38	Single	174	71	106

The relative standard deviation of each pharmacokinetic parameter after application to the abdomen averaged 50 percent, which is indicative of the considerable intersubject variability associated with transdermal drug delivery. The relative standard deviation of each pharmacokinetic parameter after application to the buttock was lower than that after application to the abdomen (for example, for C_{max} 39 percent versus 62 percent, and for C_{avg} 35 percent versus 48 percent).

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to 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 a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant proportion 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.

Adhesion

An open-label study of adhesion potentials of placebo transdermal systems that correspond to the 6.5 cm^2 and 12.5 cm^2 sizes of the Estradiol Transdermal System was conducted in 112 healthy women of 45 to 75 years of age. Each woman applied both transdermal systems weekly, on the upper outer abdomen, for 3 consecutive weeks. It should be noted that lower abdomen and upper quadrant of the buttock are the approved sites of application for the Estradiol Transdermal System.

The adhesion assessment was done visually on Days 2, 4, 5, 6, 7 of each week of transdermal system wear. A total of 1,654 adhesion observations were conducted for 333 transdermal systems of each size.

Of these observations, approximately 90 percent showed essentially no lift for both the 6.5 cm ^{2}and 12.5 cm ^{2}transdermal systems. Of the total number of transdermal systems applied, approximately 5 percent showed complete detachment for each size. Adhesion potentials of the 18.75 cm ^{2}and 25 cm ^{2}sizes of transdermal systems (0.075 mg per day and 0.1 mg per day) have not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms in Postmenopausal Women

A study of 214 women 25 to 74 years of age met the qualification criteria and were randomly assigned to one of the three treatment groups: 72 to the 0.05 mg estradiol patch, 70 to the 0.1 mg estradiol patch, and 72 to placebo. Potential participants were postmenopausal women in good general health who experienced vasomotor symptoms. Natural menopause patients had not menstruated for at least 12 months and surgical menopause patients had undergone bilateral oophorectomy at least 4 weeks before evaluation for study entry. In order to enter the 11-week treatment phase of the study, potential participants must have experienced a minimum of five moderate to severe hot flushes per week, or a minimum of 15 hot flushes of any severity per week, for 2 consecutive weeks. Women wore the patches in a cyclical fashion (three weeks on and one week off).

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

Adequate data for the analysis of efficacy was available from 191 subjects. The results are presented as the mean ± SD number of flushes in each of the 3 treatment weeks of each 4-week cycle. In the 0.05 mg estradiol group, the mean weekly hot flush rate across all treatment cycles decreased from 46 ± 6.5 at baseline to 20 ± 3 (-67 percent). The 0.1 mg estradiol group had a decline in the mean weekly hot flush rate from 52 ± 4.4 at baseline to 16 ± 2.4 (-72 percent). In the placebo group, the mean weekly hot flush rate declined from 53 ± 4.5 at baseline to 46 ± 6.5 (-18.1 percent). Compared with placebo, the 0.05 mg and 0.1 mg estradiol groups showed a statistically significantly larger mean decrease in hot flushes across all treatment cycles ($P<0.05$). When the response to treatment was analyzed for each of the three cycles of therapy, similar statistically significant differences were observed between both estradiol treatment groups and the placebo group during all treatment cycles.

In a double-blind, placebo-controlled, randomized study of 187 women receiving estradiol 0.025 mg per day or placebo continuously for up to three 28-day cycles, the estradiol 0.025 mg per day dosage was shown to be statistically better than placebo at weeks 4 and 12 for relief of both the frequency and severity of moderate to severe

vasomotor symptoms.

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

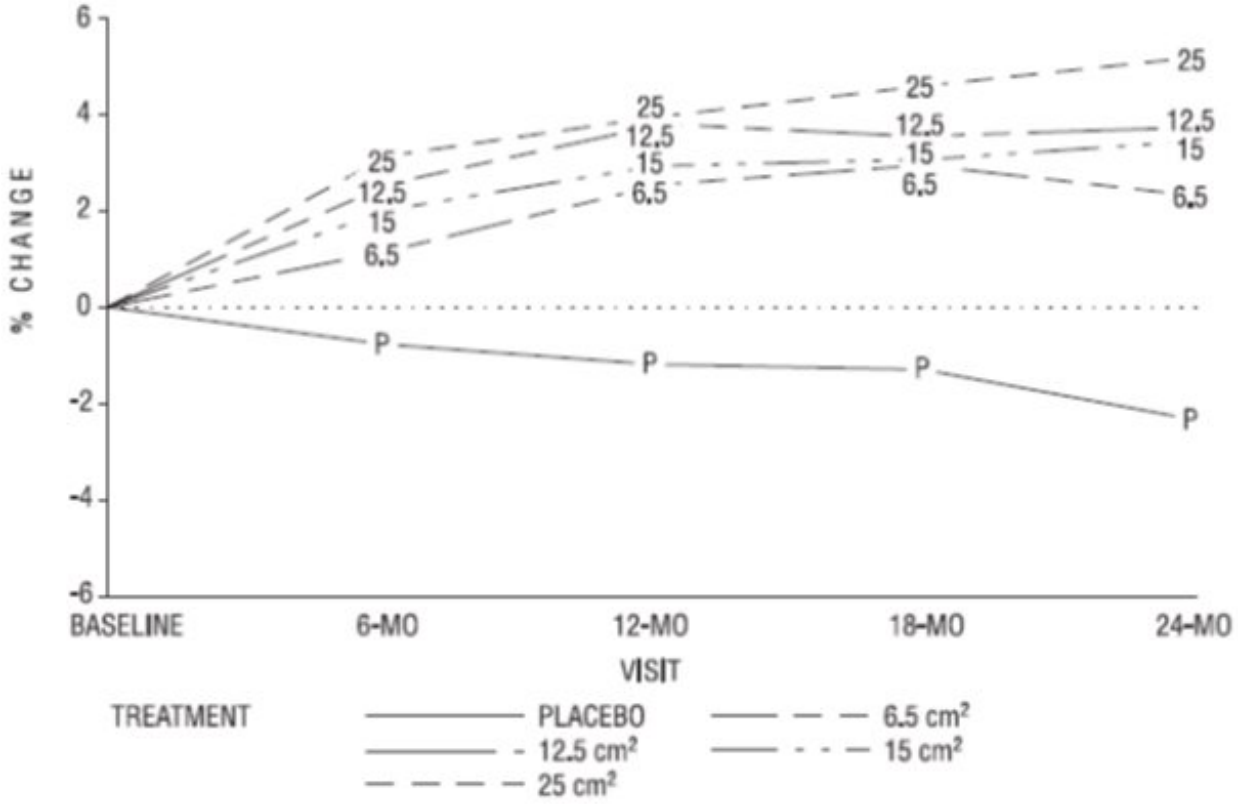
Treatment Group	Statistics	Week 4	Week 8	Week 12
E $_2$Transdermal System	N	82	84	68
	Mean	-6.45	-7.69	-7.56
	SD	4.65	4.76	4.64
Placebo	N	83	71	65
	Mean	-5.11	-5.98	-5.98
	SD	7.43	8.63	9.69
	p-value	<0.002		<0.003

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

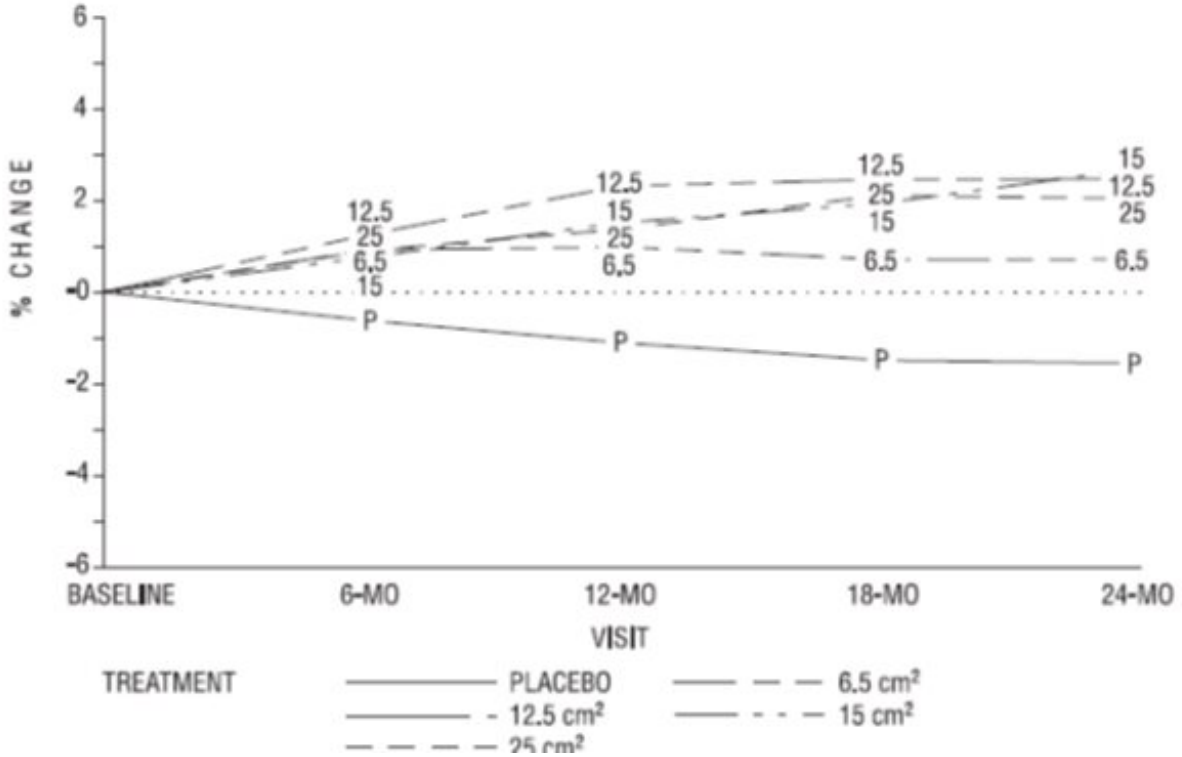
14.2 Effects on Bone Mineral Density in Postmenopausal Women

A two-year clinical trial enrolled a total of 175 healthy, hysterectomized, postmenopausal, non-osteoporotic (that is, lumbar spine bone mineral density >0.9 gm/cm ^{2}) women at 10 study centers in the United States. A total of 129 participating women were allocated to receive active treatment with 4 different doses of estradiol patches (6.5, 12.5, 15, 25 cm ^{2}) and 46 participating women were allocated to receive placebo patches. Seventy-seven percent of the randomized women (100 on active drug and 34 on placebo) contributed data to the analysis of percent change of anterior-posterior (A-P) spine BMD, the primary efficacy variable (see Figure 3). A statistically significant overall treatment effect at each timepoint was noted, implying bone preservation for all active treatment groups at all timepoints, as opposed to bone loss for placebo at all timepoints.

Figure 3: Mean Percent Change from Baseline in Lumbar Spine (A-P View) Bone Mineral Density By Treatment and Time Last Observation Carried Forward



Percent change in BMD of the total hip (see Figure 4) was also statistically significantly different from placebo for all active treatment groups. This figure is based on 74 percent of the randomized women (95 on active drug and 34 on placebo).



14.3 Women's Health Initiative Studies

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

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risk and benefits of estrogen-alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79: 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in Table 4.

Table 4: Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI [*]

Event	**Relative Risk CE vs. Placebo (95% nCI[†])**	**CE n = 5,310**	**Placebo n = 5,429**
		Absolute Risk per 10,000 Women-years	
CHD events	0.95 (0.78-1.16)	54	57
Non-fatal MIc	*0.91 (0.73-1.14)*	*40*	*43*
• *CHD death*[‡]	*1.01 (0.71-1.43)*	*16*	*16*
All strokes [‡]	1.33 (1.05-1.68)	45	33
• *Ischemic stroke*[‡]	• *1.55 (1.19-2.01)*	• *38*	• *25*
Deep vein thrombosis [‡,§]	1.47 (1.06-2.06)	23	15
Pulmonary embolism [‡]	1.37 (0.9-2.07)	14	10
Invasive breast cancer [‡]	0.80 (0.62-1.04)	28	34
Colorectal cancer [‡]	1.08 (0.75-1.55)	17	16
Hip fracture [‡]	0.65 (0.45-0.94)	12	19
Vertebral fractures [‡,§]	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures [‡,§]	0.58 (0.47-0.72)	35	59

Total fractures ‡,§	0.71 (0.64-0.80)	144	197
Death due to causes ¶,#	1.08 (0.88-1.32)	53	50
Overall mortality ‡,§	1.04 (0.88-1.22)	79	75
Global Index Þ	1.02 (0.92-1.13)	206	201

∗ Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi
† Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
‡ Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
§ Not included in "global index".
¶ Results are based on an average follow-up of 6.8 years.
# All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
Þ 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.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risks per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures. [9]The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years. See Table 4.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in the distribution of stroke subtype and severity, including fatal strokes, in women receiving estrogen-alone compared to placebo. Estrogen-alone increased the risk of ischemic stroke, and this excess risk was present in all subgroups of women examined. [10]See Table 4.

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

WHI Estrogen Plus Progestin Substudy

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

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

10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.5 percent Black, 5.4 percent Hispanic, 3.9 percent Other), are presented in Table 5 . These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 5: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years

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

Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi. Results are based on centrally adjudicated data.

* Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
† Not included in "global index".
‡ Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast

cancer.
§ All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
¶ 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.

Timing of initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for overall mortality *[HR 0.69 (95 percent CI, 0.44-1.07)]*.

14.4 Women's Health Initiative Memory Study

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

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in the study included Alzheimer’s disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]* .

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

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. Probable dementia as defined in the study included AD, VaD and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]* .

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*

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10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation.*2006;113:2425-2434.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

- Estradiol Transdermal System, 0.025 mg/day — each 6.5 cm^2 system contains 2 mg of estradiol USP
  Individual Carton of 4 systems NDC 0781-7119-54
- Estradiol Transdermal System, 0.0375 mg/day — each 9.375 cm^2 system contains 2.85 mg of estradiol USP
  Individual Carton of 4 systems NDC 0781-7122-54
- Estradiol Transdermal System, 0.05 mg/day — each 12.5 cm^2 system contains 3.8 mg of estradiol USP
  Individual Carton of 4 systems .....NDC 0781-7133-54
- Estradiol Transdermal System, 0.06 mg/day — each 15 cm^2 system contains 4.55 mg of estradiol USP
  Individual Carton of 4 systems NDC 0781-7134-54
- Estradiol Transdermal System, 0.075 mg/day — each 18.75 cm^2 system contains 5.7 mg of estradiol USP
  Individual Carton of 4 systems..... NDC 0781-7136-54
- Estradiol Transdermal System, 0.1 mg/day — each 25 cm^2 system contains 7.6 mg of estradiol USP
  Individual Carton of 4 systems .....NDC 0781-7104-54

16.2 Storage and Handling

Store at 20°C to 25°C (66°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). Do not store above 86°F (30°C).

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

Used transdermal systems still contain active hormone. To discard, fold the sticky side of the transdermal system together, place it in a sturdy child-proof container, and place this container in the trash. Used transdermal systems should not be flushed in the toilet.

17 PATIENT COUNSELING INFORMATION

Advise women to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

Vaginal Bleeding

Inform postmenopausal women to report any vaginal bleeding to their healthcare provider as soon as possible *[see Warning and Precautions (5.2)]* .

Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions (5.1, 5.2, 5.3)].*

Possible Common Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.

Patient Package Insert

Patient Information

Estradiol Transdermal System

Read this Patient Information before you start using Estradiol Transdermal System and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

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

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb).
- Report any unusual vaginal bleeding right away while you are using the Estradiol Transdermal System. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes, or dementia (decline in brain function).
- Using estrogen-alone may increase your chances of getting strokes or blood clots.

- Using estrogen-alone may increase your chance of getting dementia, based on a study of women age 65 years of age and older.
- Do not use estrogens with progestogens to prevent heart disease, heart attacks, strokes or dementia.
- Using estrogens with progestogens may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestogens may increase your chance of getting dementia, based on a study of women age 65 years of age and older.
- Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, blood clots, and dementia. Only one estrogen with progestogen product and dose have been shown to increase your chances of getting heart attacks, strokes, breast cancer, blood clots, and dementia.
- Because other products and doses have not been studied in the same way, it is not known how the use of the Estradiol Transdermal System will affect your chances of these conditions. You and your healthcare provider should talk regularly about whether you still need treatment with the Estradiol Transdermal System.

What is the Estradiol Transdermal System?

the Estradiol Transdermal System is a prescription medicine patch (transdermal system) that contains estradiol (an estrogen hormone).

What is the Estradiol Transdermal System used for?

The Estradiol Transdermal System 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 estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need to use estrogens. In other women, symptoms can be more severe.
- **Treat moderate to severe menopausal changes in and around the vagina**
- You and your healthcare provider should talk regularly about whether you still need treatment with the Estradiol Transdermal System to control these problems. If you use the Estradiol Transdermal System only to treat your menopausal changes in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.
- **Treat certain conditions in women before menopause if their ovaries do not produce enough estrogens naturally**
- **Help reduce your chances of getting osteoporosis (thin weak bones)**
- Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use the Estradiol Transdermal System only to prevent osteoporosis due to menopause, talk with your healthcare provider about whether a

different treatment or medicine without estrogens might be better for you.

You and your healthcare provider should talk regularly about whether you still need treatment with the Estradiol Transdermal System.

Who should not use the Estradiol Transdermal System?

Do not start using the Estradiol Transdermal System if you:

- **have unusual vaginal bleeding**
- Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **have been diagnosed with a bleeding disorder**
- **currently have or have had certain cancers**
- Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus (womb). If you have or have had cancer, talk with your healthcare provider about whether you should use the Estradiol Transdermal System.
- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **are allergic to the Estradiol Transdermal System or any of the ingredients in it.**See the list of ingredients in the Estradiol Transdermal System at the end of this leaflet.

Before you use the Estradiol Transdermal System, tell your healthcare provider about all of your medical conditions, including if you:

- **have any unusual vaginal bleeding**
- Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **have any other medical conditions that may become worse while you are using the Estradiol Transdermal System**
- Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face and tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **are going to have surgery or will be on bed rest.**
- Your healthcare provider will let you know if you need to stop using the Estradiol Transdermal System.
- **are pregnant or think you may be pregnant.**
- the Estradiol Transdermal System is not for pregnant women.
- **are breastfeeding**
- The hormone in the Estradiol Transdermal System can pass into your breast milk.

Tell your healthcare provider about all the medicines you take,including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may affect how the Estradiol Transdermal System works. the Estradiol Transdermal System may also affect how your other medicines work. Keep a list of your

medicines and show it to your healthcare provider and pharmacist when you get new medicine.

How should I use the Estradiol Transdermal System?

For detailed instructions, see the step-by-step instructions for using the Estradiol Transdermal System at the end of this Patient Information.

- Use the Estradiol Transdermal System exactly as your healthcare provider tells you to use it.
- the Estradiol Transdermal System is for skin use only.
- Change your Estradiol Transdermal System patch 1 time each week or every 7 days.
- Apply your Estradiol Transdermal System patch to a clean, dry area on your lower abdomen or buttocks. This area must be clean, dry, and free of powder, oil or lotion for your patch to stick to your skin.
- Apply your Estradiol Transdermal System patch to a different area of your abdomen or your buttocks each time. Do not use the same application site 2 times in the same week.
- Do not apply the Estradiol Transdermal System to your breasts.
- If you forget to apply a new Estradiol Transdermal System patch, apply a new patch as soon as possible.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about the dose you are using and whether you still need treatment with the Estradiol Transdermal System.

How to Change the Estradiol Transdermal System

- When changing the Estradiol Transdermal System, peel off the used patch slowly from the skin.
- After removal of the Estradiol Transdermal System if any adhesive residue remains on your skin, allow the area to dry for 15 minutes. Then, gently rub the area with an oil-based cream or lotion to remove the adhesive from your skin.
- Apply the new patch to a different area of your abdomen or buttocks. This area must be clean, dry, and free of powder, oil or lotion. Do not use the same site again for at least 1 week after removal of an old patch.

What are the possible side effects of the Estradiol Transdermal System?

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

Serious, but less common side effects include:

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

- new breast lumps
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue

Common side effects of the Estradiol Transdermal System include:

- headache

- breast tenderness or pain
- irregular vaginal bleeding or spotting
- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection
- redness and/or irritation at the patch placement site

These are not all the possible side effects of the Estradiol Transdermal System. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effects that bother you or do not go away.

You may report side effects to FDA at 1-800-FDA-1088. You may report side effects to Bayer Healthcare Pharmaceuticals at 1-888-842-2937.

What can I do to lower my chances of a serious side effect with the Estradiol Transdermal System?

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

How should I store and throw away the used Estradiol Transdermal System?

- Store the Estradiol Transdermal System at room temperature 68°F to 77°F (20°C to 25°C).
- Do not store the Estradiol Transdermal System patches outside of their pouches. Apply immediately upon removal from the protective pouch.
- Used patches still contain estrogen. To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet.

Keep the Estradiol Transdermal System and all medicines out of the reach of children.

General information about the safe and effective use of the Estradiol Transdermal System.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use the Estradiol Transdermal System for conditions for

which it was not prescribed. Do not give the Estradiol Transdermal patch to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about the Estradiol Transdermal System that is written for health professionals.

For more information call the toll free number 1-800-525-8747

What are the ingredients in the Estradiol Transdermal System?

Active ingredient:estradiol

Inactive ingredient:acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

INSTRUCTIONS FOR USE

Estradiol Transdermal System

Read this Patient Information before you start using the Estradiol Transdermal System and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

You will need the following supplies: See Figure A

Figure A

Step 1: Pick the days you will change your Estradiol Transdermal System.

You will need to change your patch 1 time each week or every 7 days.

Step 2. Remove the Estradiol Transdermal System patch from the pouch.

- Remove patch from its protective pouch by tearing at the notch (do not use scissors). See Figure B
- Do not remove your patch from the protective pouch until you are ready to apply it.

Figure B

Step 3. Remove the adhesive liner. See Figure C

- You will see that the Estradiol Transdermal System is an oval shaped clear patch that is attached to a thick, hard-plastic adhesive liner and covered by a clear, plastic film. See Figure C
- To apply your patch you must first remove the protective, clear plastic film that is attached to the clear thicker plastic backing. See Figure D
- There is a silver foil-sticker attached to the inside of the pouch. Do not remove the silver foil sticker from the pouch. See Figure E

Figure C **Figure D** **Figure E**

Step 4. Placing the patch on your skin.

- Apply the sticky side of the patch to 1 of the areas of skin shown below. See **Figure F**and **Figure G**
- **Do not touch**the sticky side of the patch with your fingers.

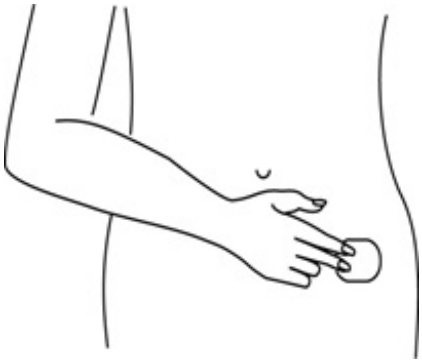

Figure F

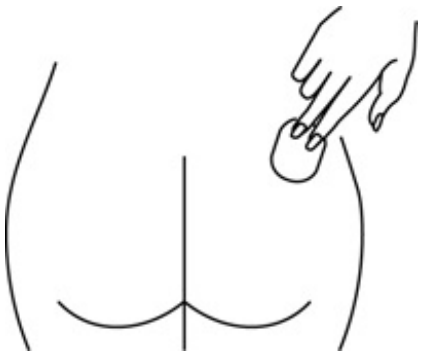

Figure G

Note:

- Avoid the waistline, since clothing and belts may cause the patch to be rubbed off.
- Do not apply the Estradiol Transdermal System to your breasts.
- Only apply the Estradiol Transdermal System to skin that is clean, dry, and free of any powder, oil, or lotion.
- Do not apply the patch to injured, burned, or irritated skin, or areas with skin conditions (such as birth marks, tattoos, or that is very hairy).

Step 5. Press the patch firmly onto your skin.

- Press the patch firmly in place with your fingers for at least 10 seconds
- Rub the edges of the patch to make sure that it will stick to your skin. (See Figure H)

Figure H

Note:

- Contact with water while you are swimming, using a sauna, bathing, or showering may cause the patch to fall off.
- If your patch falls off reapply it. If you cannot reapply the patch, apply a new patch to another area (see Figures F and G), and continue to follow your original application schedule.
- If you stop using your the Estradiol Transdermal System patch or forget to apply a new patch as scheduled, you may have spotting, or bleeding, and your symptoms may come back.

Step 6: Throwing away your used patch.

- When it is time to change your patch, remove the old patch before you apply a new patch.
- To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Do not flush used patches in the toilet.

This Patient Information and Instructions for Use have been approved by the U.S Food and Drug Administration.

Revised 9/2021

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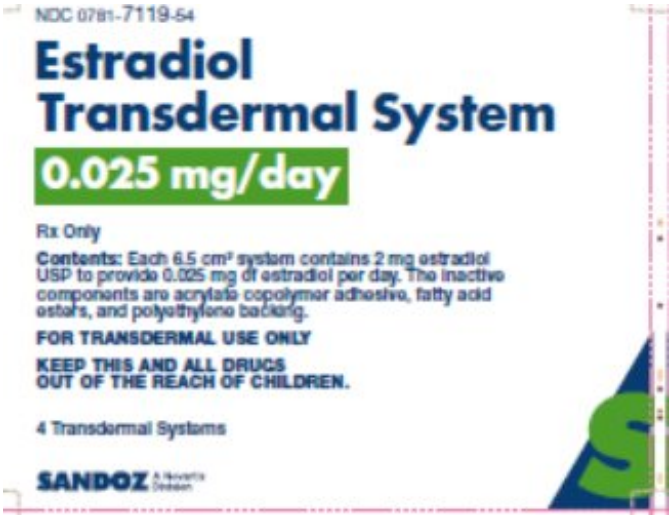
Sandoz Inc.
Princeton, NJ 08540

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7119-54
- 4 transdermal systems
- Estradiol Transdermal System
- 0.025 mg/day
- Contents: Each 6.5 cm2 system contains 2 mg estradiol USP to provide 0.025 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.
- For transdermal use only.
- Keep this and all drugs out of the reach of children.
- Rx only



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7122-54
- 4 transdermal systems
- Estradiol Transdermal System

- 0.0375 mg/day
- Contents: Each 9.375 cm2 system contains 2.85 mg estradiol USP to provide 0.0375 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.
- For transdermal use only.
- Keep this and all drugs out of the reach of children.
- Rx only

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7133-54
- 4 transdermal systems
- Estradiol Transdermal System
- 0.05 mg/day
- Contents: Each 12.5 cm2 system contains 3.8 mg estradiol USP to provide 0.05 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.
- For transdermal use only.
- Keep this and all drugs out of the reach of children.
- Rx only

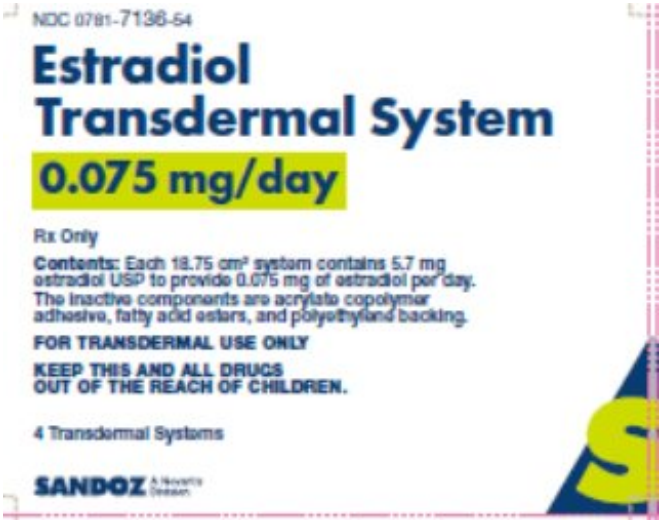
PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7134-54
- 4 transdermal systems
- Estradiol Transdermal System
- 0.06 mg/day
- Contents: Each 15 cm2 system contains 4.55 mg estradiol USP to provide 0.06 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.
- For transdermal use only.
- Keep this and all drugs out of the reach of children.
- Rx only

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7136-54
- 4 transdermal systems
- Estradiol Transdermal System
- 0.075 mg/day

- Contents: Each 18.75 cm2 system contains 5.7 mg estradiol USP to provide 0.075 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.
- For transdermal use only.
- Keep this and all drugs out of the reach of children.
- Rx only



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7104-54
- 4 transdermal systems
- Estradiol Transdermal System
- 0.1 mg/day
- Contents: Each 25 cm2 system contains 7.6 mg estradiol USP to provide 0.1 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.
- For transdermal use only.
- Keep this and all drugs out of the reach of children.
- Rx only

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-421
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.025 mg in 1 d

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:59368-421-01	4 in 1 CARTON	08/31/2018	
1		7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA020375	03/05/1999	

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-423
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.0375 mg in 1 d

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:59368-423-01	4 in 1 CARTON	08/31/2018	
1		7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA020375	05/27/2003	

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-420
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.05 mg in 1 d

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:59368-420-01	4 in 1 CARTON	08/31/2018	
1		7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA020375	12/22/1994	

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-418
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.06 mg in 1 d

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-418-01	4 in 1 CARTON	08/31/2018	
1		7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA020375	01/03/2008	

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-419
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength

ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.075 mg in 1 d

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-419-01	4 in 1 CARTON	08/31/2018	
1		7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA020375	03/23/1998	

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-422
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.1 mg in 1 d

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-422-01	4 in 1 CARTON	08/31/2018	
1		7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA020375	12/22/1994	

Labeler - Praxis, LLC (016329513)

Establishment

Name	Address	ID/FEI	Business Operations
Praxis, LLC		016329513	manufacture(59368-418, 59368-419, 59368-420, 59368-421, 59368-422, 59368-423) , label(59368-418, 59368-419, 59368-420, 59368-421, 59368-422, 59368-423) , pack(59368-418, 59368-419, 59368-420, 59368-421, 59368-422, 59368-423)

Revised: 1/2023 Praxis, LLC