



Vivelle-Dot[®]

(estradiol transdermal system)

Continuous delivery for twice-weekly application

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

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

Cardiovascular Disorders and Probable Dementia

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

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

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

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

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

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

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

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

Breast Cancer

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

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

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

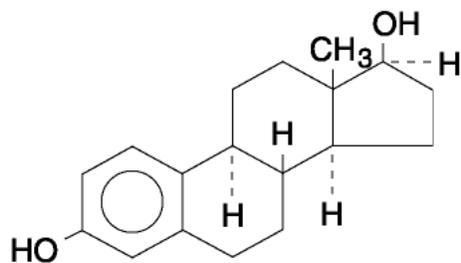
DESCRIPTION

Vivelle-Dot (estradiol transdermal system) contains estradiol in a multipolymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin.

Five dosage strengths of Vivelle-Dot are available to provide nominal *in vivo* delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5, 3.75, 5.0, 7.5, or 10.0 cm² and contains 0.39, 0.585, 0.78, 1.17, or 1.56 mg of estradiol USP, respectively. The composition of the systems per unit area is identical.

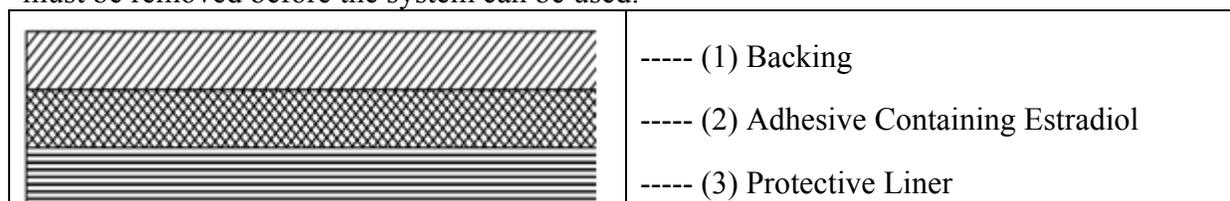
Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17 β -diol.

The structural formula is



The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.39.

Vivelle-Dot is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film (2) an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP and dipropylene glycol, and (3) a polyester release liner which 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.

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

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

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

Pharmacokinetics

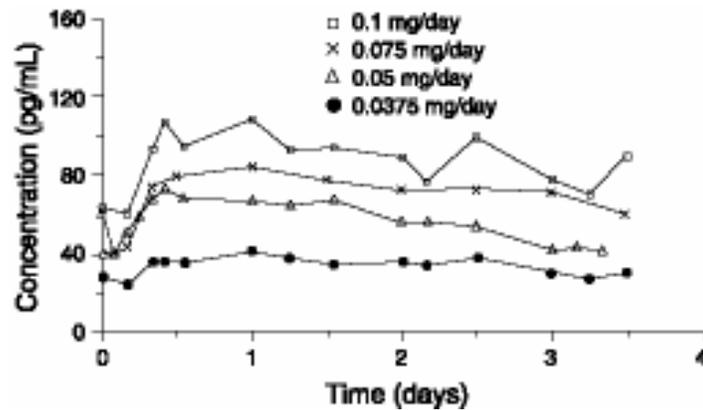
Absorption

In a multiple-dose study consisting of three consecutive system applications of the original formulation [Vivelle (estradiol transdermal system)] which was conducted in 17 healthy,

postmenopausal women, blood levels of estradiol and estrone were compared following application of these units to sites on the abdomen and buttocks in a crossover fashion. Systems that deliver nominal estradiol doses of approximately 0.0375 mg per day and 0.1 mg per day were applied to abdominal application sites while the 0.1 mg per day doses were also applied to sites on the buttocks. These systems increased estradiol levels above baseline within 4 hours and maintained respective mean levels of 25 and 79 pg/mL above baseline following application to the abdomen; slightly higher mean levels of 88 pg/mL above baseline were observed following application to the buttocks. At the same time, increases in estrone plasma concentrations averaged about 12 and 50 pg/mL, respectively, following application to the abdomen and 61 pg/mL for the buttocks. While plasma concentrations of estradiol and estrone remained slightly above baseline at 12 hours following removal of the systems in this study, results from another study show these levels to return to baseline values within 24 hours following removal of the systems.

Figure 1 illustrates the mean plasma concentrations of estradiol at steady-state during application of these patches at four different dosages.

Figure 1
Steady-State Estradiol Plasma Concentrations for Systems Applied to the Abdomen
Nonbaseline-corrected Levels



The corresponding pharmacokinetic parameters are summarized in the table below.

Table 1
Steady-State Estradiol Pharmacokinetic Parameters for
Systems Applied to the Abdomen (mean ± standard deviation)
Nonbaseline-corrected Data*

Dosage (mg/day)	C _{max} [†] (pg/mL)	C _{avg} [‡] (pg/mL)	C _{min} (84 hr) [§] (pg/mL)
0.0375	46 ± 16	34 ± 10	30 ± 10
0.05	83 ± 41	57 ± 23 [#]	41 ± 11 [#]
0.075	99 ± 35	72 ± 24	60 ± 24
0.1	133 ± 51	89 ± 38	90 ± 44
0.1 [¶]	145 ± 71	104 ± 52	85 ± 47

*Mean baseline estradiol concentration = 11.7 pg/mL

[†]Peak plasma concentration

[‡]Average plasma concentration

[§]Minimum plasma concentration at 84 hr

[#]Measured over 80 hr

[¶]Applied to the buttocks

Vivelle-Dot (estradiol transdermal system), the revised formulation with smaller system sizes, was shown to be bioequivalent to the original formulation, Vivelle (estradiol transdermal system), used in the clinical trials.

Distribution

No specific investigation of the tissue distribution of estradiol absorbed from Vivelle-Dot 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 by Cytochrome 450 isoforms CYP1A2 and CYP3A4. Estradiol undergoes further metabolism to sulfate and glucuronide conjugates. Estradiol and its metabolites are glucuronidated by UGT1A1 and UGT2B7. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The half-life values calculated after dosing with the Vivelle-Dot ranged from 5.9 to 7.7 hours. After removal of the transdermal systems, serum concentrations of estradiol and estrone returned to baseline levels within 24 hours.

Special Populations

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

Drug Interactions

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

Adhesion

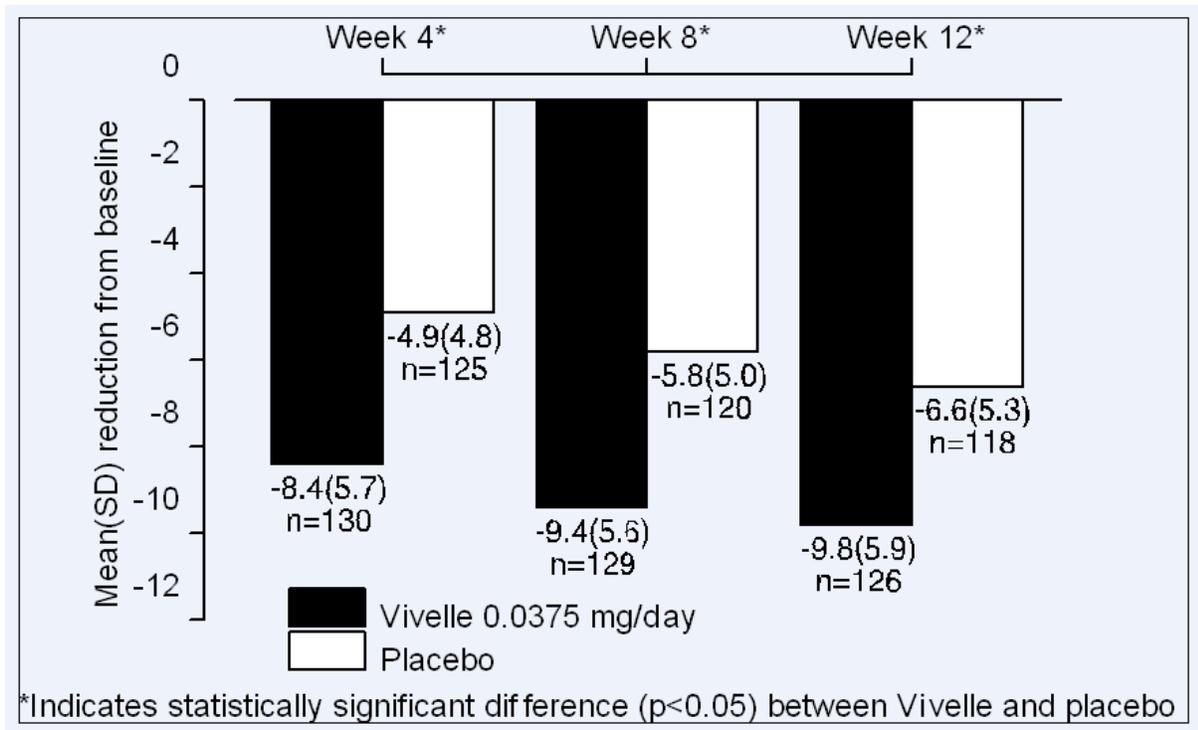
Based on combined data from three short-term clinical trials consisting of 471 observations, 85 percent of Vivelle-Dot adhered completely to the skin over the 3.5-day wear period. Three (3 percent) of the systems detached and were reapplied or replaced during the 3.5-day wear period. Approximately 80 percent of the transdermal systems evaluated in these studies were Vivelle-Dot 0.05 mg per day.

CLINICAL STUDIES

Effects on vasomotor symptoms

In a pharmacokinetic study, Vivelle-Dot was shown to be bioequivalent to Vivelle. In two controlled clinical trials with Vivelle, of 356 subjects, the 0.075 and 0.1 mg doses were superior to placebo in relieving vasomotor symptoms at Week 4, and maintained efficacy through Weeks 8 and 12 of treatment. In this original study, the 0.0375 and 0.05 mg doses, however, did not differ from placebo until approximately Week 6, therefore, an additional 12-week placebo-controlled study in 255 patients was performed with Vivelle to establish the efficacy of the lowest dose of 0.0375 mg. The baseline mean daily number of hot flushes in these 255 patients was 11.5. Results at Weeks 4, 8, and 12 of treatment are shown in Figure 2.

Figure 2
Mean (SD) change from baseline in mean daily number of flushes for
Vivelle® 0.0375 mg versus Placebo in a 12-week trial.



The 0.0375 mg dose was superior to placebo in reducing both the frequency and severity of vasomotor symptoms at Week 4 and maintained efficacy through Weeks 8 and 12 of treatment. All doses of Vivelle (0.0375 mg, 0.05 mg, 0.075 mg, and 0.1 mg) are effective for the control of vasomotor symptoms.

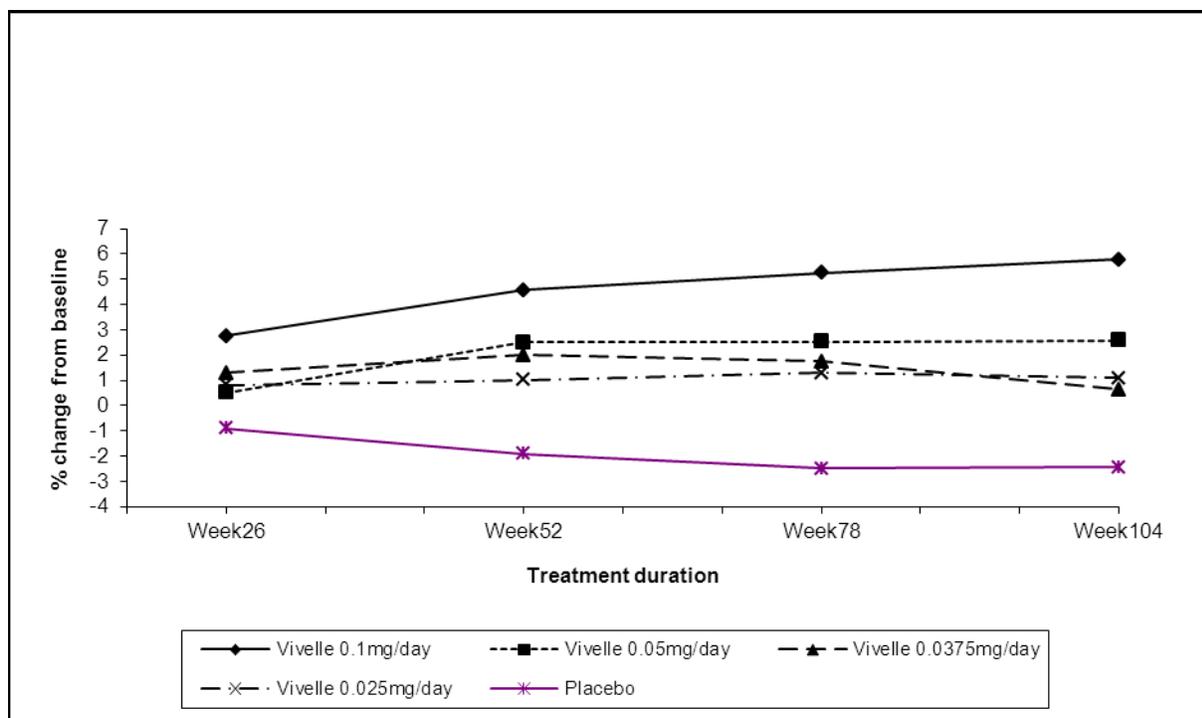
Effects on bone mineral density

Efficacy and safety of Vivelle in the prevention of postmenopausal osteoporosis have been studied in a 2-year double-blind, randomized, placebo-controlled, parallel group study. A total of 261 hysterectomized (161) and non-hysterectomized (100), surgically or naturally menopausal women (within 5 years of menopause), with no evidence of osteoporosis (lumbar spine bone mineral density within 2 standard deviations of average peak bone mass, i.e., $\geq 0.827 \text{ g/cm}^2$) were enrolled in this study; 194 patients were randomized to one of the four doses of Vivelle (0.1, 0.05, 0.0375, or 0.025 mg/day) and 67 patients to placebo. Over 2 years, study systems were applied to the buttock or the abdomen twice a week. Non-hysterectomized women received oral medroxyprogesterone acetate (2.5 mg/day) throughout the study.

The study population comprised naturally (82 percent) or surgically (18 percent) menopausal, hysterectomized (61 percent) or non-hysterectomized (39 percent) women with a mean age of 52.0 years (range 27 to 62 years); the mean duration of menopause was 31.7 months (range 2 to 72 months). Two hundred thirty-two (89 percent) of randomized subjects (173 on active drug, 59 on placebo) contributed data to the analysis of percent change from baseline in

bone mineral density (BMD) of the AP lumbar spine, the primary efficacy variable. Patients were given supplemental dietary calcium (1000 mg elemental calcium/day) but no supplemental vitamin D. There was an increase in BMD of the AP lumbar spine in all Vivelle dose groups; in contrast to this, a decrease in AP lumbar spine BMD was observed in placebo patients. All Vivelle doses were significantly superior to placebo ($p < 0.05$) at all time points with the exception of Vivelle 0.05 mg/day at 6 months. The highest dose of Vivelle was superior to the three lower doses. There were no statistically significant differences in pairwise comparisons among the three lower doses. (See Figure 3.)

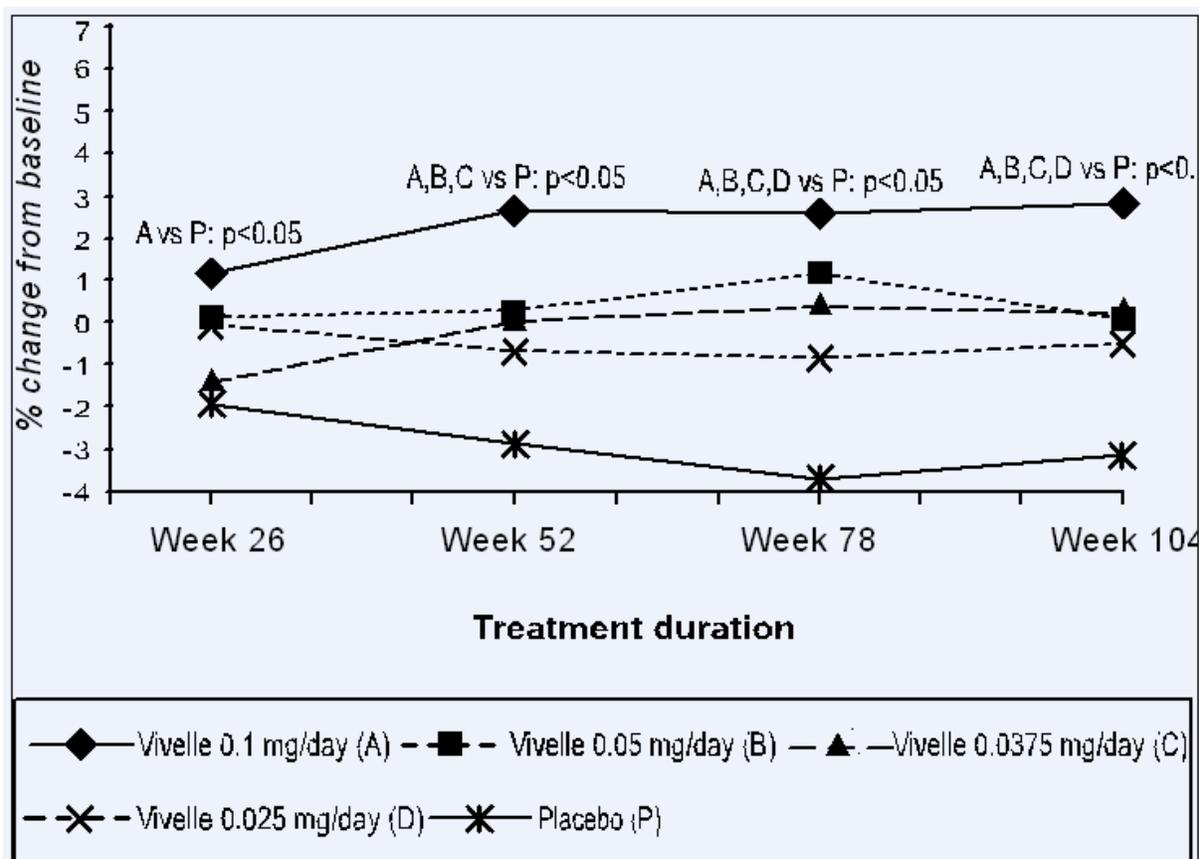
Figure 3
Bone mineral density - AP Lumbar spine
Least squares means of percentage change from baseline
All randomized patients with at least one post-baseline assessment available
with last post-baseline observation carried forward



Analysis of percent change from baseline in femoral neck BMD, a secondary efficacy outcome variable, showed qualitatively similar results; all doses of Vivelle were significantly superior to placebo ($p < 0.05$) at 24 months. The highest Vivelle dose was superior to placebo at all time points. A mixture of significant and non-significant results were obtained for the lower dose groups at earlier time points. The highest Vivelle dose was superior to the three lower doses, and there were no significant differences among the three lower doses at this skeletal site. (See Figure 4.)

Figure 4
Bone mineral density - Femoral neck
Least squares means of percentage change from baseline

**All randomized patients with at least one post-baseline assessment available
with last post-baseline observation carried forward**



The mean serum osteocalcin (a marker of bone formation) and urinary excretion of cross-link N-telopeptides of Type 1 collagen (a marker of bone resorption) decreased numerically in most of the active treatment groups relative to baseline. However, the decreases in both markers were inconsistent across treatment groups and the differences between active treatment groups and placebo were not statistically significant.

Women’s Health Initiative Studies

The Women’s Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with the MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease [(CHD) defined as nonfatal MI, silent MI, and CHD death], with invasive breast cancer as the primary adverse outcome. A “global index” included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in 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 risks and benefits of estrogen-alone in predetermined primary endpoints. Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in Table 2.

**TABLE 2. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE
SUBSTUDY OF WHI^a**

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

^a Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

^b Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

^c Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

^d Not included in “global index”.

^e Results are based on an average follow-up of 6.8 years.

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

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

For those outcomes included in the WHI “global index” that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures. The absolute excess risk of events included in the “global index” was a 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 2.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant differences in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined. See Table 2.

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

WHI Estrogen Plus Progestin Substudy

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

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

Results of the estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79, 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 3. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 3. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN PLUS PROGESTIN SUBSTUDY OF WHI AT AN AVERAGE OF 5.6 YEARS^{a,b}

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

^a Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

^b Results are based on centrally adjudicated data.

^c Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

^d Not included in “global index”.

^e Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.

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

Event	Relative Risk	CE/MPA	Placebo
	CE/MPA vs. Placebo (95% nCI ^c)	n = 8,506	n = 8,102
		Absolute Risk per 10,000 Women-Years	

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

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

Women’s Health Initiative Memory Study

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

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer’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, Probable Dementia**, and **PRECAUTIONS, Geriatric Use**.)

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

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

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

INDICATIONS AND USAGE

Vivelle-Dot is indicated in the:

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

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

CONTRAINDICATIONS

Vivelle-Dot is contraindicated in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected or history of breast cancer.
3. Known or suspected estrogen-dependent neoplasia.
4. Active DVT, PE, or a history of these conditions.
5. Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions

6. Known anaphylactic reaction or angioedema or hypersensitivity to Vivelle-Dot.
7. Liver impairment or disease.
8. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.
9. Known or suspected pregnancy.

WARNINGS

See **BOXED WARNINGS**.

1. Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

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

a. Stroke

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

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

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

b. Coronary Heart Disease

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

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

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

In postmenopausal women with documented heart disease (n = 2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in the HERS, the HERS II, and overall.

c. Venous Thromboembolism

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

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

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

2. Malignant Neoplasms

a. Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg)-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80). (See **CLINICAL STUDIES**.)

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA.

In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 per cent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA 92.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade, and hormone receptor status did not differ between the groups. (See **CLINICAL STUDIES**.)

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to

return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

c. Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies and some report no association.

3. Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

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

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

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

4. Gallbladder Disease

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

5. Hypercalcemia

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

6. Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

7. Hereditary Angioedema

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

PRECAUTIONS

1. A. General

1. Addition of a progestin when a woman has not had a hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

2. Elevated blood pressure

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

3. Hypertriglyceridemia

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

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

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

5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as cardiac or renal impairment, warrant careful observation when estrogen-alone is prescribed.

7. Hypocalcemia

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

8. Exacerbation of endometriosis

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

9. Exacerbation of other conditions

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

1. B. Patient Information

Physicians are advised to discuss the **PATIENT INFORMATION** leaflet with women for whom they prescribe Vivelle-Dot.

C. Laboratory Tests

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

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

1. D. Drug-Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex; and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased TBG leading to increased circulating total thyroid hormone levels, 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. Women on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum, for example, corticosteroid-binding globulin (CBG), SHBG, leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma high-density lipoprotein (HDL) and HDL₂ cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

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

1. F. Pregnancy

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

1. G. Nursing Mothers

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

H. Pediatric Use

Estrogen therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding.

I. Geriatric Use

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

The Women's Health Initiative Studies

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

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

The Women's Health Initiative Memory Study

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

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

ADVERSE REACTIONS

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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The following adverse events have been reported with Vivelle-Dot therapy:

Table 4
Summary of Most Frequently Reported Adverse Experiences/Medical Events
Regardless of Relationship Reported at a Frequency \geq 5 Percent

Vivelle 0.025 mg/day [†] (N=47) N (%)	Vivelle 0.0375 mg/day [†] (N=130) N (%)	Vivelle 0.05 mg/day [†] (N=103) N (%)	Vivelle 0.075 mg/day [†] (N=46) N (%)	Vivelle 0.1 mg/day [†] (N=132) N (%)	Placebo (N=157) N (%)
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Gastrointestinal disorders

Constipation	2 (4.3)	5 (3.8)	4 (3.9)	3 (6.5)	2 (1.5)	4 (2.5)
Dyspepsia	4 (8.5)	12 (9.2)	3 (2.9)	2 (4.3)	0	10 (6.4)
Nausea	2 (4.3)	8 (6.2)	4 (3.9)	0	7 (5.3)	5 (3.2)
General disorders and administration site conditions***						
Influenza-like illness	3 (6.4)	6 (4.6)	8 (7.8)	0	3 (2.3)	10 (6.4)
Pain NOS*	0	8 (6.2)	0	2 (4.3)	7 (5.3)	7 (4.5)
Infections and infestations						
Influenza	4 (8.5)	4 (3.1)	6 (5.8)	0	10 (7.6)	14 (8.9)
Nasopharyngitis	3 (6.4)	16 (12.3)	10 (9.7)	9 (19.6)	11 (8.3)	24 (15.3)
Sinusitis NOS*	4 (8.5)	17 (13.1)	13 (12.6)	3 (6.5)	7 (5.3)	16 (10.2)
Upper respiratory tract infection NOS*	3 (6.4)	8 (6.2)	11 (10.7)	4 (8.7)	6 (4.5)	9 (5.7)
Investigations						
Weight increased	4 (8.5)	5 (3.8)	2 (1.9)	2 (4.3)	0	3 (1.9)
Musculoskeletal and connective tissue disorders						
Arthralgia	0	11 (8.5)	4 (3.9)	2 (4.3)	5 (3.8)	9 (5.7)
Back pain	4 (8.5)	10 (7.7)	9 (8.7)	4 (8.7)	14 (10.6)	10 (6.4)
Neck pain	3 (6.4)	4 (3.1)	4 (3.9)	0	6 (4.5)	2 (1.3)
Pain in limb	0	10 (7.7)	7 (6.8)	2 (4.3)	6 (4.5)	9 (5.7)
Nervous system disorders						
Headache NOS*	7 (14.9)	35 (26.9)	32 (31.1)	23 (50.0)	34 (25.8)	37 (23.6)
Sinus headache	0	12 (9.2)	5 (4.9)	5 (10.9)	2 (1.5)	8 (5.1)
Psychiatric disorders						
Anxiety NEC**	3 (6.4)	5 (3.8)	0	0	2 (1.5)	4 (2.5)
Depression	5 (10.6)	4 (3.1)	7 (6.8)	0	4 (3.0)	6 (3.8)
Insomnia	3 (6.4)	6 (4.6)	4 (3.9)	2 (4.3)	2 (1.5)	9 (5.7)
Reproductive system and breast disorders						
Breast tenderness	8 (17.0)	10 (7.7)	8 (7.8)	3 (6.5)	17 (12.9)	0
Dysmenorrhea	0	0	0	3 (6.5)	0	0
Intermenstrual bleeding	3 (6.4)	9 (6.9)	6 (5.8)	0	14 (10.6)	7 (4.5)
Respiratory, thoracic and mediastinal disorders						
Sinus congestion	0	4 (3.1)	3 (2.9)	3 (6.5)	6 (4.5)	7 (4.5)
Vascular disorders						
Hot flushes NOS*	3 (6.4)	0	3 (2.9)	0	0	6 (3.8)
Hypertension NOS*	2 (4.3)	0	3 (2.9)	0	0	2 (1.3)

† Represents milligrams of estradiol delivered daily by each system

* NOS represents not otherwise specified

** NEC represents not elsewhere classified

*** Application site erythema and application site irritation were observed in a small number of patients (3.2% or less of patients across treatment groups.)

Postmarketing Experience

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

Genitourinary System

Vaginal hemorrhage and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, uterine leiomyomata, vaginitis, vaginal discharge, ovarian cancer, endometrial hyperplasia.

Breast

Enlargement, pain, nipple discharge, fibrocystic breast changes, breast cancer.

Cardiovascular

Deep venous thrombosis, pulmonary embolism, thrombophlebitis.

Gastrointestinal

Nausea, vomiting, abdominal cramps, bloating, cholelithiasis, liver function tests abnormal, diarrhea.

Skin

Erythema multiforme, erythema nodosum, loss of scalp hair, hirsutism, pruritis, rash.

Eyes

Intolerance to contact lenses.

Central Nervous System

Migraine, dizziness, chorea, nervousness, affect liability, irritability.

Miscellaneous

Decrease in weight, reduced carbohydrate tolerance, edema, arthralgias, leg cramps, changes in libido, purpura, hypersensitivity.

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

The adhesive side of Vivelle-Dot should be placed on a clean, dry area of the trunk of the body (including the abdomen or buttocks). *Vivelle-Dot should not be applied to the breasts.* Vivelle-Dot 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 event that a system should fall off, the same system may be reapplied. If the same system cannot be reapplied, a new system should be applied to another location. In either case, the original treatment schedule should be continued. If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The new patch should be applied on the original treatment schedule. The interruption of treatment in women taking Vivelle-Dot might increase the likelihood of breakthrough bleeding, spotting and recurrence of symptoms.

Initiation of Therapy

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen-alone or in combination with a progestin, should be with the lowest effective dose and the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (for example at 3-month to 6-month intervals) to determine whether treatment is still necessary. For a woman with a uterus, adequate diagnostic measures, such as directed or random endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal genital bleeding.

Patients should be started at the lowest dose. The lowest effective dose of Vivelle-Dot has not been determined for any indication. For treatment of moderate to severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, start therapy with Vivelle-Dot 0.0375 mg per day applied to the skin twice weekly. For the prevention of postmenopausal osteoporosis, start therapy with Vivelle-Dot 0.025 mg per day applied to the skin twice weekly. The dosage may be adjusted as necessary. Reproductive system-associated adverse events were encountered more frequently in the highest dose group (0.1 mg per day) than in other active treatment groups or in placebo-treated patients.

In women not currently taking oral estrogens or in women switching from another estradiol transdermal therapy, treatment with Vivelle-Dot may be initiated at once. In women who are currently taking oral estrogens, treatment with Vivelle-Dot should be initiated 1 week after withdrawal of oral hormone therapy, or sooner if menopausal symptoms reappear in less than 1 week.

Therapeutic Regimen

Vivelle-Dot may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, Vivelle-Dot may be given on a cyclic schedule (for example, 3 weeks on drug followed by 1 week off drug).

HOW SUPPLIED

Vivelle-Dot (estradiol transdermal system), 0.025 mg per day - each 2.5 cm² system contains 0.39 mg of estradiol USP for nominal* delivery of 0.025 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0078-0365-42

Carton of 3 Patient Calendar Packs of 8 Systems.....NDC 0078-0365-45

Vivelle-Dot (estradiol transdermal system), 0.0375 mg per day - each 3.75 cm² system contains 0.585 mg of estradiol USP for nominal* delivery of 0.0375 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0078-0343-42

Carton of 3 Patient Calendar Packs of 8 Systems.....NDC 0078-0343-45

Vivelle-Dot (estradiol transdermal system), 0.05 mg per day - each 5.0 cm² system contains 0.78 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0078-0344-42

Carton of 3 Patient Calendar Packs of 8 Systems.....NDC 0078-0344-45

Vivelle-Dot (estradiol transdermal system), 0.075 mg per day - each 7.5 cm² system contains 1.17 mg of estradiol USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0078-0345-42

Carton of 3 Patient Calendar Packs of 8 Systems.....NDC 0078-0345-45

Vivelle-Dot (estradiol transdermal system), 0.1 mg per day - each 10.0 cm² system contains 1.56 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0078-0346-42

Carton of 3 Patient Calendar Packs of 8 Systems.....NDC 0078-0346-45

*See **DESCRIPTION**.

Store at controlled room temperature at 25°C (77°F).

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

REV: 05/2013

PATIENT INFORMATION
Vivelle-Dot (vyvel-dot)
(estradiol transdermal system)

Read this Patient Information before you start using Vivelle-Dot 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 medical condition or your treatment.

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

- Using estrogen-alone increases your chance of getting cancer of the uterus (womb).

Report any unusual vaginal bleeding right away while you are using Vivelle-Dot. 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 65 years of age or older.
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes, or dementia.
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- You and your healthcare provider should talk regularly about whether you still need treatment with Vivelle-Dot.

What is Vivelle-Dot?

Vivelle-Dot is a prescription medicine patch (Transdermal System) that contains estradiol (an estrogen hormone). When applied to the skin as directed below, Vivelle-Dot releases estrogen through the skin into the bloodstream.

What is Vivelle-Dot used for?

Vivelle-Dot is used after menopause to:

- **Reduce moderate to severe hot flashes**

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

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe.

- **Treat 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 Vivelle-Dot to control these problems. If you use Vivelle-Dot 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 Vivelle-Dot only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

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

You and your healthcare provider should talk regularly about whether you should continue treatment with Vivelle-Dot.

Who should not use Vivelle-Dot?

Do not start using Vivelle-Dot 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.

- **currently have or have had certain cancers**

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

- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **have been diagnosed with a bleeding disorder**
- **are allergic to Vivelle-Dot or any of its ingredients**

See the list of ingredients in Vivelle-Dot at the end of this leaflet.

- **think you may be pregnant**

Vivelle-Dot is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not use Vivelle-dot if the test is positive and talk to your healthcare provider.

What should I tell my healthcare provider before I use Vivelle-Dot? Before you use Vivelle-Dot, tell your healthcare provider if you:

- **have any unusual vaginal bleeding**

Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **have any other medical conditions**

Your healthcare provider may need to check you more carefully if you have certain conditions such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **are going to have surgery or will be on bed rest**

Your healthcare provider will let you know if you need to stop using Vivelle-Dot.

- **are breast feeding**

The hormone in Vivelle-Dot can pass into your breast milk.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Vivelle-Dot works. Vivelle-Dot may also affect how other medicines work.

How should I use Vivelle-Dot?

For detailed instructions, see the step-by-step instructions for using Vivelle-Dot at the end of this Patient Information.

- a. Use Vivelle-Dot exactly as your healthcare provider tell you to use it
- b. Vivelle-Dot is for skin use only
- c. Change your Vivelle-Dot patch 2 times a week or every 3 to 4 days
- d. Apply your Vivelle-Dot patch to a clean, dry area of your lower abdomen. This area must be clean, dry, and free of powder, oil or lotion for your pouch to stick to your skin
- e. Apply your Vivelle-Dot patch to a different area of your abdomen each time. Do not use the same application site 2 times in the same week
- f. Do not apply Vivelle-Dot to your breasts
- g. If you forget to apply a new Vivelle-Dot patch, you should apply a new patch as soon as possible.
- h. You and your healthcare provider should talk regularly (every 3 to 6 months) about your dose and whether you still need treatment with Vivelle-Dot.

How to Change Vivelle-Dot

- When changing the patch, peel off the used patch slowly from the skin
- After removal of Vivelle-Dot, patients usually have either no adhesive residue or light adhesive residue. If any adhesive residue remains on your skin after removing the patch, allow the area to dry for 15 minutes. Then, gently rub the area with oil or lotion to remove the adhesive from your skin
- Keep in mind, **the new patch must be applied to a different area of your lower abdomen.** This area must be clean, dry, cool and free of powder, oil or lotion.

What are the possible side effects of Vivelle-Dot?

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

Serious, but less common side effects include:

- heart attack

- stroke
- blood clots
- dementia
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- high blood pressure
- high blood sugar
- gallbladder disease
- liver problems
- changes in your thyroid hormone levels
- Enlargement of benign tumors ("fibroids")

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

Less serious, but common side effects include:

- headache
- breast pain

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

These are not all the possible side effects of Vivelle-Dot. For more information, ask your healthcare provider or pharmacist for advice about side effects. Tell your healthcare provider if you have any side effect that bothers you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may report side effects to Noven at 1-800-445-8070.

What can I do to lower my chances of getting a serious side effect with Vivelle-Dot?

- Talk with your healthcare provider regularly about whether you should continue using Vivelle-Dot
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you

The addition of a progestin is generally recommended for 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 Vivelle-Dot
- 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 of getting heart disease

Ask your healthcare provider for ways to lower your chances of getting heart disease.

How should I store and throw away used Vivelle-Dot patches:

- Store at room temperature 68°F to 77°F (20°C to 25°C)

- Do not store Vivelle-Dot 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 VIVELLE-DOT and all medicines out of the reach of children

General information about safe and effective use of Vivelle-Dot

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

This leaflet provides a summary of the most important information about Vivelle-Dot. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about Vivelle-Dot that is written for health professionals. For more information, go to www.vivelle-dot.com or call the toll-free number Noven Pharmaceuticals Inc at 1-800-445-8070.

What are the ingredients in Vivelle-Dot?

Active ingredient: estradiol

Inactive ingredient: a translucent polyolefin film, acrylic and silicone adhesives, oleyl alcohol, NF, povidone, USP, dipropylene glycol and a polyester release liner.

Application Instructions for Vivelle-Dot (estradiol transdermal system)

1. Determine Your Schedule for Your Twice-a-Week Application

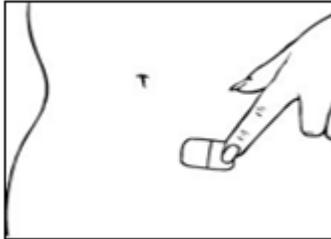
VIVELLE dot [®]	
(estradiol transdermal system)	
Change your patch only on these two days:	
<input type="checkbox"/> Sun / Wed	<input type="checkbox"/> Thu / Sun
<input type="checkbox"/> Mon / Thu	<input type="checkbox"/> Fri / Mon
<input type="checkbox"/> Tue / Fri	<input type="checkbox"/> Sat / Tue
<input type="checkbox"/> Wed / Sat	

- Decide upon which two days you will change your patch.
- Your Vivelle-Dot (estradiol transdermal system) individual carton contains a calendar card printed on its inner flap. Mark the two-day schedule you plan to follow on your carton's inner flap.
- Be consistent.
- If you forget to change your patch on the correct

date, apply a new one as soon as you remember.

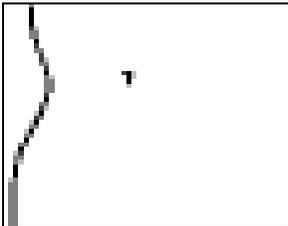
- No matter what day this happens, stick to the schedule you have marked on the inner flap of your carton (your calendar card).

2. Where to Apply Vivelle-Dot



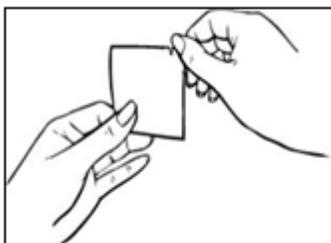
- Apply patch to a dry area of the skin of the trunk of the body, including the lower abdomen, or buttocks. Avoid the waistline, since clothing may cause the patch to rub off.
- Do not apply patch to breasts.
- When changing your patch, based on your twice-a-week schedule, apply your new patch to a different site. Do not apply a new patch to that same area for at least one week.

3. Before You Apply Vivelle-Dot

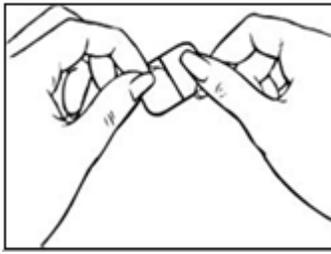


- **Make sure your skin is:**
- Clean (freshly washed), dry and cool.
- Free of any powder, oil, moisturizer or lotion.
- Free of cuts or irritations (rashes or other skin problems).

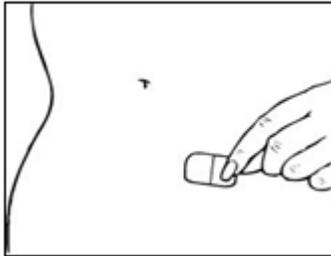
4. How to Apply Vivelle-Dot



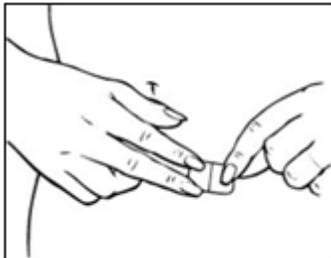
- Each patch is individually sealed in a protective pouch.
- Tear open the pouch at the tear notch (do not use scissors).
- Remove the patch.



- **Apply the patch immediately after removing from pouch.**



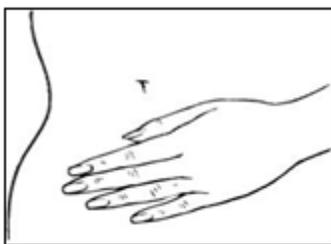
- Holding the patch with the rigid protective liner facing you, remove **half** of the liner, which covers the sticky surface of the patch.



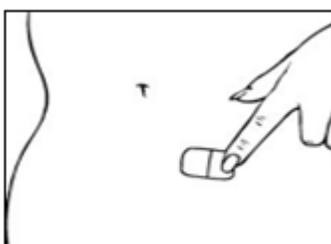
- **Avoid touching the sticky side of the patch with your fingers.**
- Using the other half of the rigid protective liner as a handle, apply the sticky side of the patch to the selected area of the abdomen or buttocks



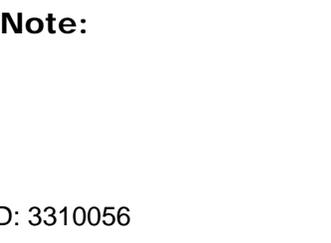
- Press the sticky side of the patch firmly into place.
- Smooth it down.
- While still holding the sticky side down, fold back the other half of the patch.



- Grasp an edge of the remaining protective liner and gently pull it off.
- **Avoid touching the sticky side of the patch with your fingers.**



- Press the entire patch firmly into place with the palm of your hand.
- Continue to apply pressure, with the palm of your hand over the patch, for approximately 10 seconds.



- Make sure that the patch is properly adhered to your skin.
- Go over the edges with your finger to ensure good contact around the patch.

Note:

- Showering will not cause your patch to fall off
- If your patch falls off reapply it. If you cannot reapply the patch, apply a new patch to another area and continue to follow your original placement schedule
- If you stop using your Vivelle-Dot patch or forget to apply a new patch as scheduled, you may have spotting, or bleeding, and recurrence of symptoms.

Throwing away your used patch

- When it 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 the container in the trash. Used patches should not be flushed in the toilet.

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

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