

NDA 20-323/S-017, S-025, S-030

Page 3



Vivelle[®]

estradiol transdermal system

Continuous delivery for twice-weekly application

Rx only

Prescribing Information

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER.

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

CARDIOVASCULAR AND OTHER RISKS

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

The Women’s Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**). Other doses of conjugated estrogens with medroxyprogesterone, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar for all estrogens and estrogen-progestin combinations. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

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

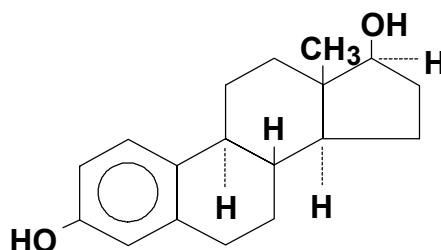
NDA 20-323/S-017, S-025, S-030

Page 4

Five systems are available to provide nominal in vivo delivery of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via skin of average permeability. Each corresponding system having an active surface area of 7.25, 11.0, 14.5, 22.0 or 29.0 cm² contains 2.17, 3.28, 4.33, 6.57, or 8.66 mg of estradiol USP, respectively. The composition of the systems per unit area is identical.

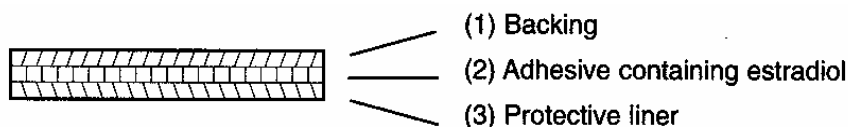
Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17 β -diol.

The structural formula is



The molecular formula of estradiol is C₁₈H₂₄O₂. The molecular weight is 272.39.

The Vivelle system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent flexible film consisting of an ethylene vinyl alcohol copolymer film, a polyurethane film, urethane polymer and epoxy resin, (2) an adhesive formulation containing estradiol USP, acrylic adhesive, polyisobutylene, ethylene vinyl acetate copolymer, 1,3 butylene glycol, styrene-butadiene rubber, oleic acid NF, lecithin, propylene glycol, bentonite NF, mineral oil USP, and dipropylene glycol, and (3) a polyester release liner that 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 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

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

NDA 20-323/S-017, S-025, S-030
Page 5

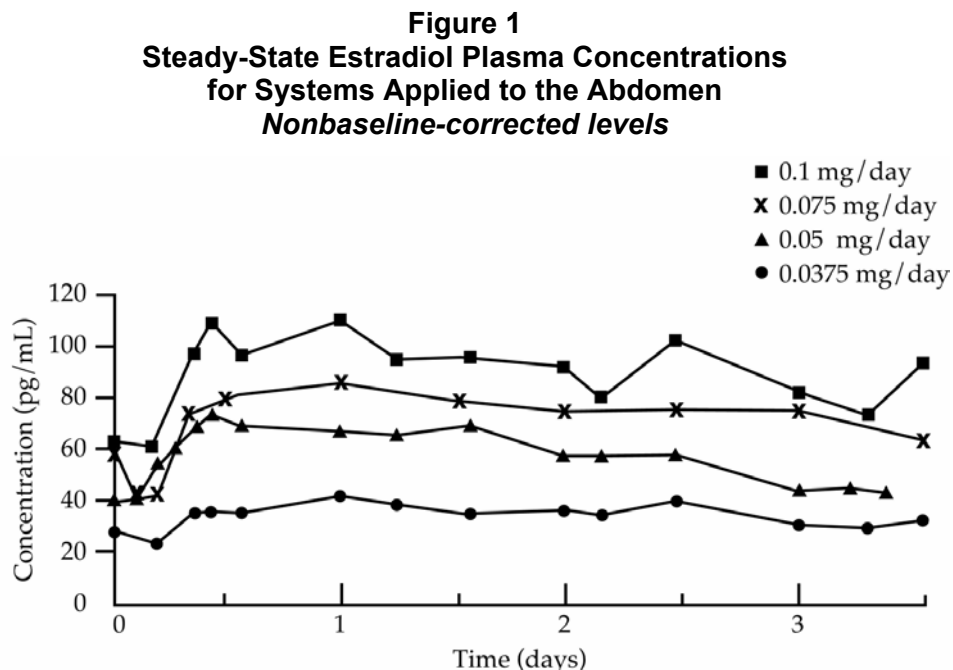
Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

Absorption

In a multiple-dose study consisting of three consecutive patch applications of the Vivelle 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. Patches that deliver nominal estradiol doses of approximately 0.0375 mg/day and 0.1 mg/day were applied to abdominal application sites while the 0.1 mg/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 patches in this study, results from another study show these levels to return to baseline values within 24 hours following removal of the patches.

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



The corresponding pharmacokinetic parameters are summarized in the table below.

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

NDA 20-323/S-017, S-025, S-030

Page 6

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

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG), and, to a lesser extent, albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugated, 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. Studies conducted with the Vivelle system show the drug has an apparent mean half-life of 4.4 ± 2.3 hours. After removal of the transdermal systems, serum concentrations of estradiol and estrone returned to baseline levels within 24 hours.

Special Populations

Vivelle was only investigated in postmenopausal women.

Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital,

NDA 20-323/S-017, S-025, S-030
Page 7

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.

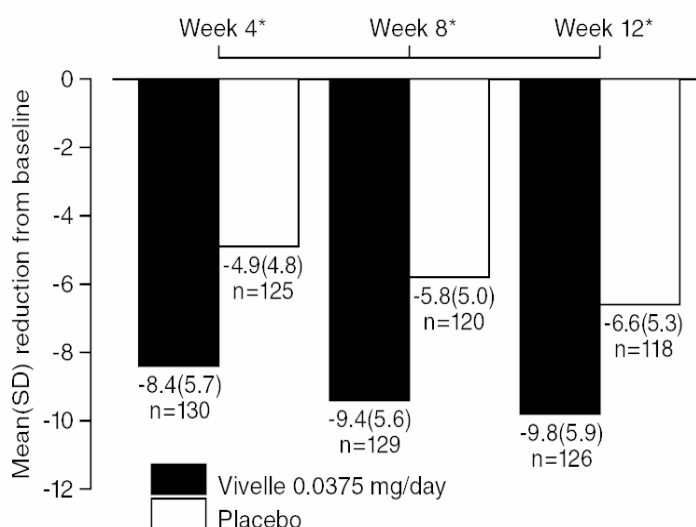
Adhesion

Data showing the number of systems in controlled studies that required replacement due to inadequate adhesion is not available.

Clinical Studies

In two controlled clinical trials 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 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 the figure below. (See 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.



*Indicates statistically significant difference ($p < 0.05$) between Vivelle and placebo

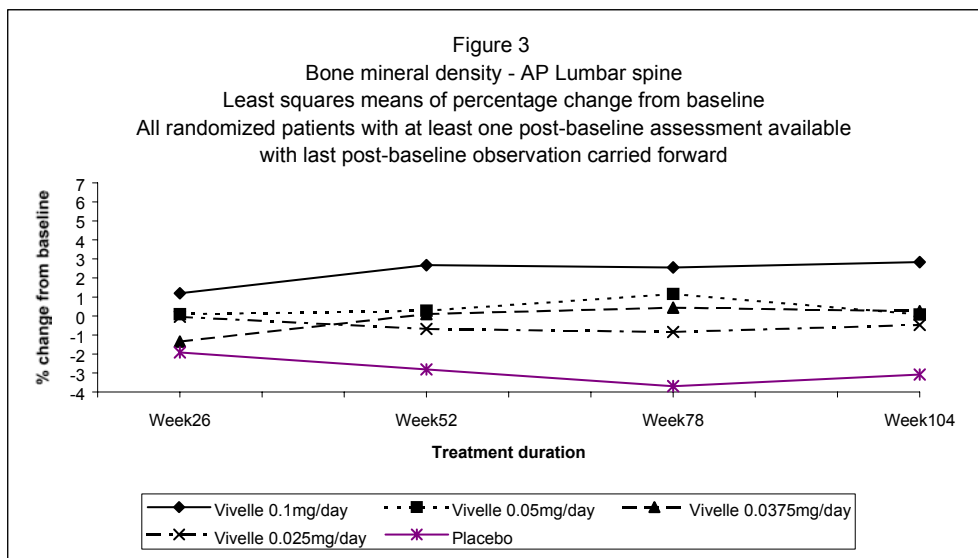
The 0.0375 mg dose was superior to placebo in reducing both the frequency and severity of vasomotor symptoms at Week 4 and maintained efficacy through Weeks 8 and 12 of treatment. The following doses of Vivelle: 0.0375 mg, 0.05 mg, 0.075 mg, and 0.1 mg, are effective for the control of vasomotor symptoms.

Efficacy and safety of the Vivelle system in the prevention of postmenopausal osteoporosis have been studied in a 2-year double-blind, randomized, placebo-controlled, parallel group study. A

NDA 20-323/S-017, S-025, S-030
Page 8

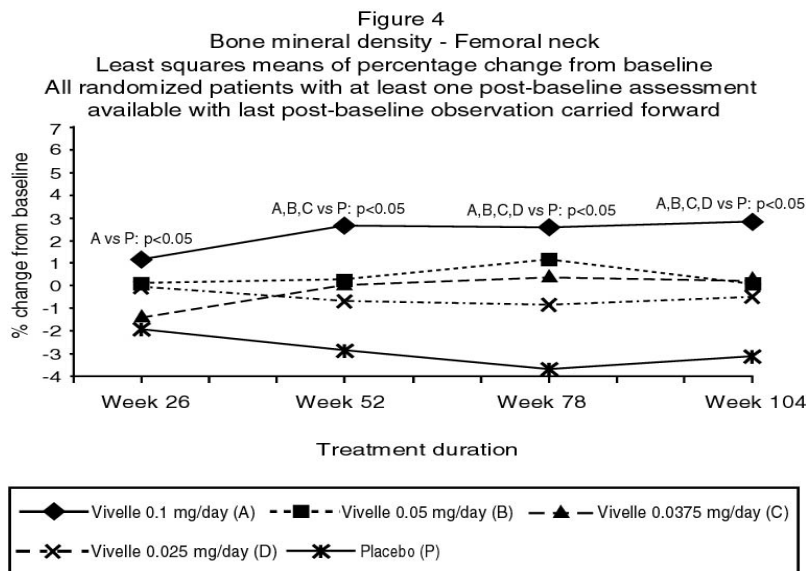
total of 261 hysterectomized (161) and non-hysterectomized (100), surgically or naturally menopausal women (within 5 years of menopause), with no evidence of osteoporosis (lumbar spine bone mineral density within 2 standard deviations of average peak bone mass, i.e., $\geq 0.827 \text{ g/cm}^2$) were 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%) or surgically (18%) menopausal, hysterectomized (61%) or nonhysterectomized (39%) 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%) 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.)



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.)

NDA 20-323/S-017, S-025, S-030
Page 9



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

The CE-only substudy is continuing and results have not been reported. The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79, 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 2 below.

Table 2, RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI^a

Event ^c	Relative Risk CE/MPA vs. Placebo at 5.2 Years (95% CI*)	Placebo n= 8102	CE/MPA n= 8506
		Absolute Risk per 10,000 person-years	
CHD events	1.29 (1.02-1.63)	30	37

NDA 20-323/S-017, S-025, S-030
Page 10

Non-fatal MI	1.32 (1.02-1.72)	23	30
CHD death	1.18 (0.70-1.97)	6	7
Invasive breast cancer ^b	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global index ^c	1.15 (1.03-1.28)	151	170
Deep vein thrombosis ^d	2.07 (1.49-2.87)	13	26
Vertebral fractures ^d	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures ^d	0.77 (0.69-0.86)	170	131

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

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

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

^d not included in Global index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the “global index”, absolute excess risks per 10,000 person-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,00 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the “global index” was 19 per 10,000 person-years. There was no difference between the groups in terms of all-cause mortality (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

INDICATIONS AND USAGE

Vivelle is indicated in the following:

1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.

NDA 20-323/S-017, S-025, S-030

Page 11

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

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

CONTRAINDICATIONS

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

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

WARNINGS

See **BOXED WARNINGS**.

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

1. Cardiovascular disorders

Estrogen and estrogen/progestin therapy have been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and

NDA 20-323/S-017, S-025, S-030

Page 12

pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

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

a. Coronary heart disease and stroke

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

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

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

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

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

b. Venous thromboembolism (VTE)

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

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

NDA 20-323/S-017, S-025, S-030
Page 13

10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

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

2. Malignant Neoplasms

a. Endometrial cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

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

b. Breast cancer

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

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

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens with or without a progestin. This association was reanalyzed in original data from 51 studies that involved various doses and types of estrogens, with and without progestins. In the reanalysis, an increased risk of having breast cancer diagnosed became apparent after about 5 years of continued treatment,

NDA 20-323/S-017, S-025, S-030
Page 14

and subsided after treatment had been discontinued for 5 years or longer. Some later studies have suggested that postmenopausal treatment with estrogens and progestin increase the risk of breast cancer more than treatment with estrogen alone.

A postmenopausal woman without a uterus who requires estrogen should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. All postmenopausal women should receive yearly breast exams by a health care provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.

3. Gallbladder Disease

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

4. Hypercalcemia

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

5. Visual abnormalities

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

PRECAUTIONS

A. General

1. **Addition of a progestin when a woman has not had a hysterectomy.** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include:
 - a. A possible increased risk of breast cancer
 - b. Adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL)
 - c. Impairment of glucose tolerance
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,

NDA 20-323/S-017, S-025, S-030

Page 15

placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. **Familial hyperlipoproteinemia.** In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.
 4. **Impaired liver function.** Although transdermally administered estrogen therapy avoids first-pass hepatic metabolism, estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.
 5. **Hypothyroidism.** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.
 6. **Fluid retention.** Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.
 7. **Hypocalcemia.** Estrogens should be used with caution in individuals with severe hypocalcemia.
 8. **Ovarian cancer.** Use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with estrogen/progestin combination therapy in postmenopausal women.
 9. **Exacerbation of endometriosis.** Endometriosis may be exacerbated with administration of estrogen therapy.
 10. **Exacerbation of other conditions.** Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria and should be used with caution in women with these conditions.
- B. Patient Information.** Physicians are advised to discuss the **Patient Information** leaflet with patients for whom they prescribe Vivelle.
- C. Laboratory Tests.** Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradiol, FSH).
- D. Drug/Laboratory Test Interactions.**
1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex; and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III; decreased antithrombin III activity;

NDA 20-323/S-017, S-025, S-030

Page 16

increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

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

E. Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See **BOXED WARNINGS, CONTRAINDICATIONS, and WARNINGS.**)

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

G. Nursing Mothers. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Vivelle is administered to a nursing woman.

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

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

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding. (See **INDICATIONS and DOSAGE AND ADMINISTRATION.**)

I. Geriatric Use. The safety and effectiveness in geriatric patients have not been established.

NDA 20-323/S-017, S-025, S-030
Page 17

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 adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The following adverse events have been reported with Vivelle therapy:

Table 3
Summary of Most Frequently Reported Adverse Experiences/Medical Events
Regardless of Relationship Reported at a Frequency ≥ 5%

	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 (%)		
Gastrointestinal disorders								
(1.5)	4 (2.5)		Constipation	2 (4.3)	5 (3.8)	4 (3.9)	3 (6.5)	2
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								
(3.1)	6 (5.8)	0	10 (7.6)	14 (8.9)		Influenza	4 (8.5)	4
Nasopharyngitis	3 (6.4)	16 (12.3)	10 (9.7)	9 (19.6)	11 (8.3)	24 (15.3)		
16 (10.2)		Sinusitis NOS*	4 (8.5)	17 (13.1)	13 (12.6)	3 (6.5)	7 (5.3)	
infection NOS*	Upper respiratory tract 3 (6.4)	8 (6.2)	11 (10.7)	4 (8.7)	6 (4.5)	9 (5.7)		
Investigations								
3 (1.9)		Weight increased		4 (8.5)	5 (3.8)	2 (1.9)	2 (4.3)	0
Musculoskeletal and connective tissue disorders								
(5.7)		Arthralgia	0	11 (8.5)	4 (3.9)	2 (4.3)	5 (3.8)	9
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)		

NDA 20-323/S-017, S-025, S-030

Page 18

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*								

† 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.)

The following additional adverse reactions have been reported with estrogens:

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

NDA 20-323/S-017, S-025, S-030

Page 19

8. Miscellaneous. Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; anaphylactoid/anaphylactic reactions including urticaria and angioedema; hypocalcemia; exacerbation of asthma; increased triglycerides.

Post-Marketing Adverse Events

Although a causal relationship with Vivelle has not been established, adverse events reported from marketing experience include: isolated reports of anaphylaxis, rare elevated liver function tests, and reports of leg pain.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

The adhesive side of the Vivelle system should be placed on a clean, dry area of the trunk of the body (including the abdomen or buttocks). *The Vivelle system should not be applied to the breasts.* The Vivelle system should be replaced twice weekly. The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the event that a system should fall off, the same system may be reapplied. If necessary, a new system may be applied. In either case, the original treatment schedule should be continued. 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 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, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g. 3-month to 6-month intervals) to determine whether treatment is still necessary (See **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Patients should be started at the lowest dose. For treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, start therapy with Vivelle estradiol transdermal system 0.0375 mg/day applied to the skin twice weekly. For the prevention of

NDA 20-323/S-017, S-025, S-030

Page 20

postmenopausal osteoporosis, the minimum dose that has been shown to be effective is 0.025 mg/day. The dosage may be adjusted as necessary. Reproductive system-associated adverse events were encountered more frequently in the highest dose group (0.1 mg/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 the Vivelle estradiol transdermal system may be initiated at once. In women who are currently taking oral estrogens, treatment with the Vivelle estradiol transdermal system 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 may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, Vivelle may be given continuously or on a cyclic schedule (e.g., three weeks on drug followed by one week off drug) with a progestin.

HOW SUPPLIED

Vivelle estradiol transdermal system 0.025 mg/day – each 7.25 cm² system contains 2.17 mg of estradiol USP for nominal* delivery of 0.025 mg of estradiol per day.

Patient Calendar Pack of 8 systems.....NDC 0078-0348-42

Vivelle estradiol transdermal system 0.0375 mg/day - each 11.0 cm² system contains 3.28 mg of estradiol USP for nominal* delivery of 0.0375 mg of estradiol per day.

Patient Calendar Pack of 8 systems.....NDC 0083-2325-08

Vivelle estradiol transdermal system 0.05 mg/day - each 14.5 cm² system contains 4.33 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 systems.....NDC 0083-2326-08

Vivelle estradiol transdermal system 0.075 mg/day - each 22.0 cm² system contains 6.57 mg of estradiol USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 systems.....NDC 0083-2327-08

Vivelle estradiol transdermal system 0.1 mg/day - each 29.0 cm² system contains 8.66 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 systems.....NDC 0083-2328-08

*See DESCRIPTION

Do not store above 30°C (86°F). Do not store unpouched. Apply immediately upon removal from the protective pouch.

REV:

NDA 20-323/S-017, S-025, S-030
Page 21

PATIENT INFORMATION

Vivelle[®]

estradiol transdermal system

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

The Vivelle (estradiol transdermal system) patch that your health care provider has prescribed for you releases small amounts of an estrogen hormone through the skin.

This leaflet describes the risks and benefits of treatment with Vivelle. Vivelle is not for everyone. Talk to your health care provider if you have any questions or concerns about this medication.

What is the most important information I should know about Vivelle?

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

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

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

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

What is Vivelle?

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

What is Vivelle used for?

Vivelle 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 in life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed

NDA 20-323/S-017, S-025, S-030
Page 22

during an operation before natural menopause takes place. The sudden drop in estrogen levels causes “surgical menopause.”

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest or sudden strong feelings of heat and sweating (“hot flashes” or “hot flushes”). In some women the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your health care provider should talk regularly about whether you still need treatment with Vivelle.

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

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

- **treat certain conditions in which a young woman’s ovaries do not produce enough estrogens naturally.**
- **help reduce your chances of getting osteoporosis (thin weak bones).**

Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use Vivelle only to prevent osteoporosis from menopause, talk with your health care provider about whether a different treatment or medicine without estrogens might be better for you. You and your health care provider should talk regularly about whether you should continue with Vivelle. Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your health care provider before starting them.

Who should not take Vivelle?

Do not start taking Vivelle if you:

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

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

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

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

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

Tell your health care provider:

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

NDA 20-323/S-017, S-025, S-030
Page 23

endometriosis, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

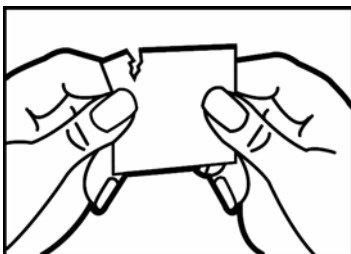
- **about all the medicines you take**, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Vivelle works. Vivelle may also affect how other medicines work.
- **if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens.

How should I take Vivelle?

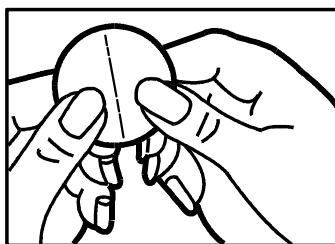
Estrogens should be used only as long as needed and at the lowest possible dose that works. You and your health care provider should talk regularly (for example every 3 to 6 months) about whether you still need treatment with Vivelle.

How and Where to Apply Vivelle

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

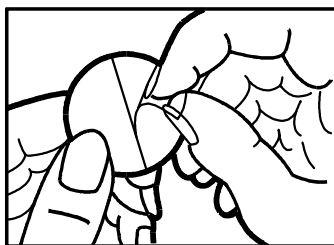


A stiff protective liner covers the adhesive side of the system - the side that will be placed against your skin. This liner must be removed before applying the system. Hold the unit with the protective liner facing you.

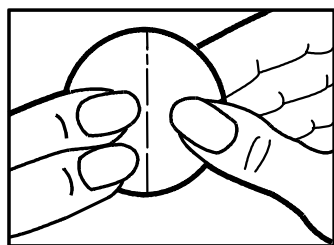


Peel off one side of the protective liner and discard it. Try to avoid touching the sticky side of the system with your fingers.

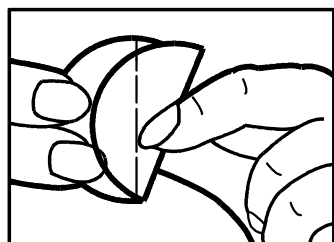
NDA 20-323/S-017, S-025, S-030
Page 24



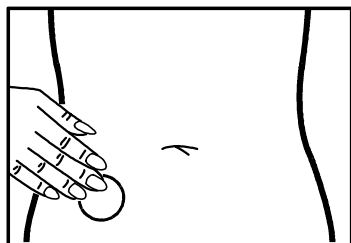
Using the other half of the liner as a handle, apply the sticky side of the system to a dry area of the skin on the trunk of the body (including the abdomen or buttocks). Press the sticky side on the skin and smooth down.



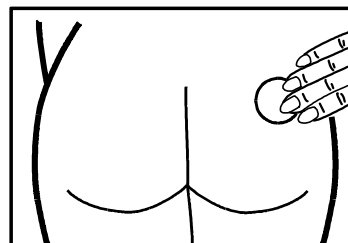
Fold back the remaining side of the system. Grasp the straight edge of the protective liner and pull it off the system.



Press the system firmly in place.



OR



Some women may find that it is more comfortable to wear Vivelle on the buttocks. *Do not apply Vivelle to your breasts.* The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub the system off. Apply the system immediately after opening the pouch and removing the protective liner. Press the system firmly in

NDA 20-323/S-017, S-025, S-030
Page 25

place with the palm of your hand for about 10 seconds, making sure there is good contact, especially around the edges.

The Vivelle system should be worn continuously until it is time to replace it with a new system. You may wish to experiment with different locations when applying a new system, to find ones that are most comfortable for you and where clothing will not rub on the system.

When to Apply Vivelle

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

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

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

What are the possible side effects of estrogens?

Less common but serious side effects include:

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

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

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

NDA 20-323/S-017, S-025, S-030

Page 26

— Vomiting

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

Common side effects include:

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

Other side effects include:

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

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

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

- Talk with your health care provider regularly about whether you should continue taking Vivelle.
- See your health care provider right away if you get vaginal bleeding while taking Vivelle.
- Have a breast exam and mammogram (breast X-ray) every year unless your health care provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your health care provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Vivelle

NDA 20-323/S-017, S-025, S-030

Page 27

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Vivelle for conditions for which it was not prescribed. Do not give Vivelle to other people, even if they have the same symptoms you have. It may harm them. **Keep Vivelle out of the reach of children.**

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

What are the ingredients in Vivelle?

The Vivelle system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent flexible film consisting of an ethylene vinyl alcohol copolymer film, a polyurethane film, urethane polymer and epoxy resin, (2) an adhesive formulation containing estradiol USP, acrylic adhesive, polyisobutylene, ethylene vinyl acetate copolymer, 1,3 butylene glycol, styrene-butadiene rubber, oleic acid NF, lecithin, propylene glycol, bentonite NF, mineral oil USP, and dipropylene glycol, and (3) a polyester release liner that 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.

REV: Printed in U.S.A.



Distributed by
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

©Novartis

REFERENCES:

1. Chetkowski RJ, Meldrum DR, Steingold KA, et al. Biologic effects of transdermal estradiol. N Engl J Med 1986; 314: 1615-1620.
2. Breckenridge A. Enzyme induction in humans. Clinical aspects-an overview. Pharmacol Ther. 1987; 33: 95-99.

NDA 20-323/S-017, S-025, S-030
Page 28

3. Samsioe G. The role of ERT/HRT. Best Practice & Research Clinical Obstetrics and Gynaecology 2002; 16: 371-381.