Vivelle®

Approved February 25, 2000

(estradiol transdermal system)

Continuous delivery for twice-weekly application

Rx only

Prescribing Information

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

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 no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

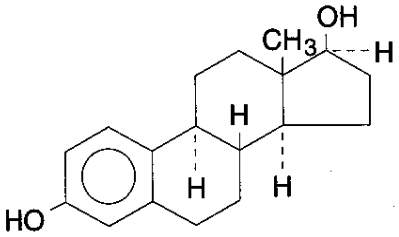
DESCRIPTION

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

Four systems are available to provide nominal in vivo delivery of 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 11.0, 14.5, 22.0 or 29.0 cm^2 contains 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-3,17ß-diol.

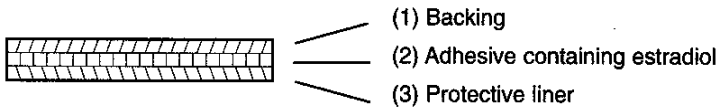
The structural formula is



The molecular formula of estradiol is $C_{18}H_{24}O_2$. 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, acrylic adhesive, polyisobutylene, ethylene vinyl acetate copolymer, 1,3 butylene glycol, styrene-butadiene rubber, oleic acid, lecithin, propylene glycol, bentonite,

mineral oil, 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

Vivelle system provides systemic estrogen replacement therapy by releasing estradiol, the major estrogenic hormone secreted by the human ovary. 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.

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

Pharmacokinetics

Absorption

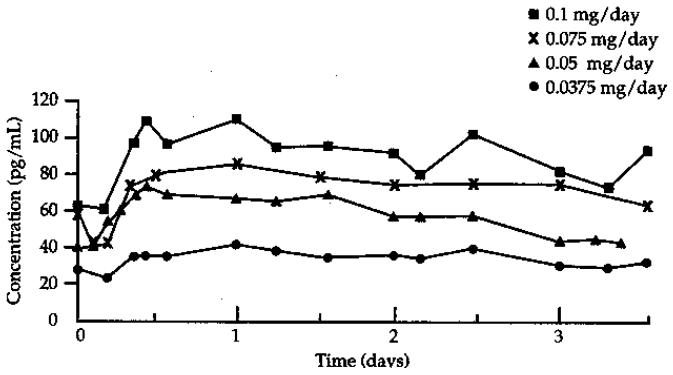
In a multiple-dose study consisting of three consecutive patch applications of the Vivelle system, which was conducted in 17 healthy, postmenopausal women, blood levels of estradiol and estrone were compared following application of these units to sites on the abdomen and buttocks in a crossover fashion. 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 graph illustrates the mean plasma concentrations of estradiol at steady-state during application of these patches at four different dosages.

Steady-State Estradiol Plasma Concentrations

for Systems Applied to the Abdomen

Nonbaseline-corrected levels



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*

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. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone binding globulin (SHBG), and to a lesser degree to 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.

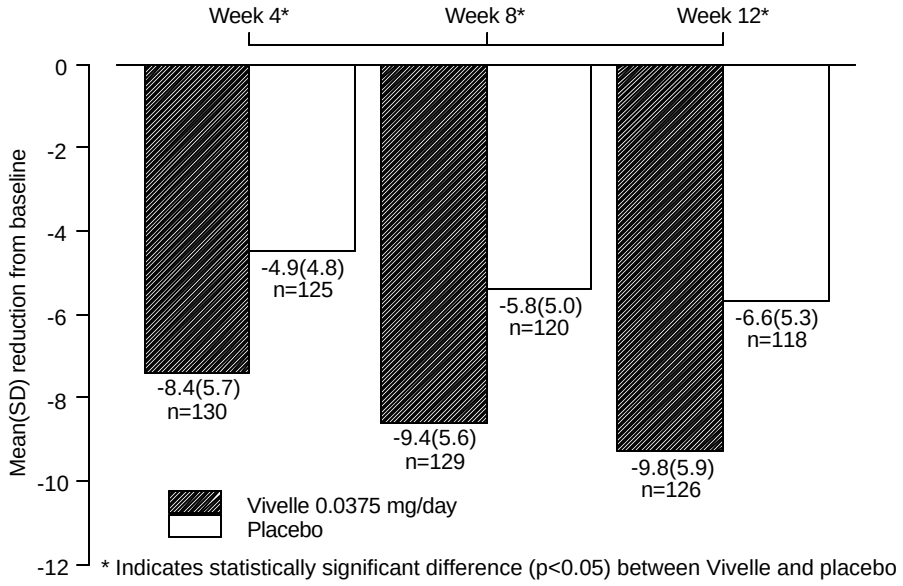
Special Populations
The Vivelle system has been studied only in postmenopausal women.

Drug Interactions
No drug interaction studies were conducted with the Vivelle system.

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. 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.

Figure **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.

INDICATIONS AND USAGE

Vivelle® (estradiol transdermal system) is indicated in the following:

1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

CONTRAINDICATIONS

Patients with known hypersensitivity to any of the components of the therapeutic system should not use Vivelle.

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

1. Known or suspected pregnancy (see PRECAUTIONS). Estrogen may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding.

3. Known or suspected cancer of the breast.
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders, or a documented history of these conditions.

WARNINGS

1. *Induction of Malignant Neoplasms.*

a. *Breast cancer*. Some studies have suggested a possible increased incidence of breast cancer in women taking estrogen therapy at higher doses for prolonged periods of time, especially in excess of 10 years. The majority of studies, however, have not shown an association with the usual doses used for estrogen replacement therapy. Women on this therapy should have regular breast examinations and should be instructed in breast self-examination.

b. *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 10 years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study, a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk, but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

c. *Congenital reproductive tract disorders*. Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders. In female offspring, there is an increased risk of vaginal adenosis, squamous cell dysplasia of the cervix, and clear cell vaginal cancer later in life; in males, urogenital and possibly testicular abnormalities. Although some of these changes are benign, it is not known whether they are precursors of malignancy.

2. *Gallbladder Disease***.** Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in postmenopausal women receiving oral estrogen replacement therapy, similar to the 2-fold increase previously noted in users of oral contraceptives.

3. *Cardiovascular Disease***.** 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. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

4. *Elevated Blood Pressure***.** Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use, especially if high doses are used. Ethinyl estradiol and conjugated estrogens have been

shown to increase renin substrate. In contrast to these oral estrogens, transdermally administered estradiol does not affect renin substrate.

5. *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.

PRECAUTIONS

General

1. *Addition of a Progestin.* Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily in an estrogen/progestin continuous regimen have reported a lower incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphologic and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

   There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include:

   (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL), which could diminish the purported cardioprotective effect of estrogen therapy (see PRECAUTIONS, below);

   (2) impairment of glucose tolerance; and

   (3) Possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiologic data are available to address this point (see PRECAUTIONS, below).

   The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

2. *Cardiovascular Risk*. A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

   In recent years, many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy *without added progestins* and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

   (1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected

for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

(2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.

(3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiologic evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS, above).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

3. *Physical Examination.* A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.
4. *Hypercoagulability***.** Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. Epidemiological studies, which employed primary orally administered estrogen products, have suggested that hormone replacement therapy (HRT) is associated with an increased relative risk of developing venous thromboembolism (VTE), e.g., deep venous thrombosis or pulmonary embolism. Risk/benefit should therefore be carefully weighed in consultation with the patient when prescribing any form of HRT to women with a risk factor for VTE.
5. *Familial Hyperlipoproteinemia***.** Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

6. *Fluid Retention***.** Because estrogens may cause some degree of fluid retention, conditions that might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.
7. *Uterine Bleeding and Mastodynia*. Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.
8. *Impaired Liver Function***.** Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

Information for the Patient

See text of Patient Package Insert, which appears after the HOW SUPPLIED section.

Laboratory Tests

Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable.

Drug/Laboratory Test Interactions

Some of these drug/laboratory test interactions have been observed only with estrogen progestin combinations (oral contraceptives):

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex; and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.
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 triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.
7. Reduced serum folate concentration.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Pregnancy Category X

Estrogens should not be used during pregnancy. There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

Nursing Mothers

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

Geriatric Use

The safety and effectiveness in geriatric patients (over age 65) have not been established.

ADVERSE REACTIONS

See WARNINGS and Boxed Warning regarding the potential adverse effects on the fetus, the induction of malignant neoplasms, gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia.

The most commonly reported systemic adverse event to the Vivelle system in controlled clinical trials was headache. This occurred in approximately 36% of patients treated with active systems and in 30% of patients treated with placebo. The most common topical adverse events in these trials were erythema and pruritus at the application site. Most cases were considered mild. Fewer than 5% of patients on active drug at the final visit of the study had reactions of greater than mild intensity. Rash

was reported in approximately 5% of patients treated with active systems and in approximately 4% of patients treated with placebo in these trials. Two patients out of 356 were discontinued from the trials due to skin irritation/erythema.

The following additional adverse reactions have been reported with estrogen therapy:

1. *Genitourinary system*. Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting; increase in size of uterine leiomyomata; vaginal candidiasis; change in amount of cervical secretion.
2. *Breasts.* Tenderness, enlargement.
3. *Gastrointestinal*. Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; gallbladder disease.
4. *Skin*. Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.
5. *Eyes*. Steepening of corneal curvature; intolerance to contact lenses.
6. *Central Nervous System*. Headache, migraine, dizziness; mental depression; chorea.
7. *Miscellaneous*. Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

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.

Initiation of Therapy

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. In order to use the lowest dosage necessary for the control of symptoms, decisions to increase dosage should not be made until after the first month of therapy. Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

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 replacement 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 0.0375 mg/day - each 11.0 cm^2 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
Carton of 6 Patient Calendar Packs of 8 systems ..... NDC 0083-2325-62
Carton of 24 systems ..... NDC 0083-2325-25

Vivelle estradiol transdermal system 0.05 mg/day - each 14.5 cm^2 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
Carton of 6 Patient Calendar Packs of 8 systems ..... NDC 0083-2326-62
Carton of 24 systems ..... NDC 0083-2326-25

Vivelle estradiol transdermal system 0.075 mg/day - each 22.0 cm^2 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
Carton of 6 Patient Calendar Packs of 8 systems ..... NDC 0083-2327-62
Carton of 24 systems ..... NDC 0083-2327-25

Vivelle estradiol transdermal system 0.1 mg/day - each 29.0 cm^2 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
Carton of 6 Patient Calendar Packs of 8 systems ..... NDC 0083-2328-62
Carton of 24 systems ..... NDC 0083-2328-25

*See DESCRIPTION

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

1/00

Information for the Patient

Vivelle®
(estradiol transdermal system)

Rx Only

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE").

If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

INTRODUCTION

Your doctor has prescribed the Vivelle system for the treatment of your menopausal symptoms. During menopause, production of estrogen hormones by your body decreases well below the amounts normally produced during your fertile years. In many women this decrease in estrogen production causes uncomfortable symptoms, most noticeably hot flushes and sleep disturbance. Estrogens can be given to reduce or eliminate these symptoms.

The Vivelle system that your doctor has prescribed for you releases small amounts of estradiol through the skin in a continuous way. Estradiol is the same hormone that your ovaries produce abundantly before menopause. The dose of estradiol you require will depend upon your individual response. The dose is adjusted by the size of the Vivelle system used; the systems are available in four sizes.

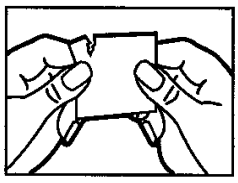
INFORMATION ABOUT VIVELLE

How Vivelle works

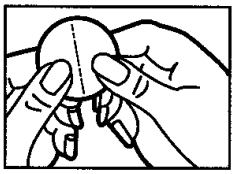
Vivelle contains estradiol. When applied to the skin as directed below, the Vivelle system releases estradiol, which flows through the skin into the bloodstream.

How and Where to Apply Vivelle

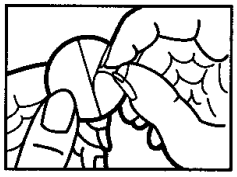
Each system is individually sealed in a protective pouch. Tear open this pouch at the indentation (do not use scissors) and remove the system.



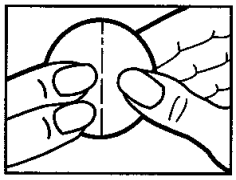
A stiff protective liner covers the adhesive side of the system–the side that will be placed against your skin. This liner must be removed before applying the system. Hold the unit with the protective liner facing you.



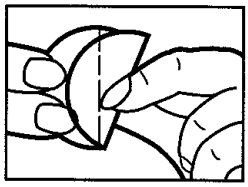
Peel off one side of the protective liner and discard it. Try to avoid touching the sticky side of the system with your fingers.



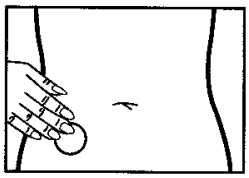
Using the other half of the liner as a handle, apply the sticky side of the system to a dry area of the skin on the trunk of the body (including the abdomen or buttocks). Press the sticky side on the skin and smooth down.



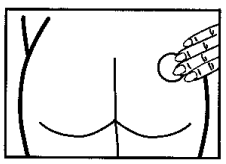
Fold back the remaining side of the system. Grasp the straight edge of the protective liner and pull it off the system.



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 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 on the back to help you remember a schedule. Mark the 2-day schedule you plan to follow. Always change the system on the 2 days of the week you have marked.

When changing the system, remove the used 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.

Benefits of treatment with Vivelle

Regular use of the Vivelle twice weekly offers relief of moderate-to-severe symptoms of menopause.

Small quantities of the naturally occurring hormone estradiol are absorbed through the skin from the Vivelle system, ensuring a continuous supply of circulating hormone in the body.

USES OF ESTROGEN

To reduce moderate or severe menopausal symptoms. Estrogens are hormones produced by the ovaries. The decrease in the amount of estrogen that occurs in all women, usually between ages 45 and 55, causes the menopause. Sometimes the ovaries are removed by an operation, causing "surgical menopause." When the amount of estrogen begins to decrease, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest or sudden intense episodes of heat and sweating ("hot flashes"). The use of drugs containing estrogens can help the body adjust to lower estrogen levels.

Some women have only mild menopausal symptoms, or none at all, and do not need estrogen therapy for these particular symptoms. Other women may need estrogens for a few months while their bodies adjust to lower estrogen levels. For the treatment of menopausal symptoms only, most women need estrogen replacement therapy for no longer than 6 months.

To treat vulvar and vaginal atrophy (itching, burning, dryness in or around the vagina, difficulty or burning on urination) *associated with menopause.*

To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.

WHEN ESTROGENS SHOULD NOT BE USED

During pregnancy. If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Boxed Warning). Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.

If you have had cancer. Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you have or have ever had cancer of the breast or uterus.

If you have any circulation problems. Estrogen therapy should be used only after consultation with your doctor and only in recommended doses. Patients with current or past abnormal blood clotting should not use estrogens (see DANGERS OF ESTROGENS, below).

When they are ineffective. During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.

After childbirth or when breastfeeding a baby. Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see DANGERS OF ESTROGEN, below).

If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your healthcare provider.

DANGERS OF ESTROGENS

Cancer of the uterus. The risk of developing cancer of the uterus gets higher the longer estrogens are used and when larger doses are taken. One study showed that when estrogens are discontinued, this increased risk of cancer seems to fall off quickly. Three other studies showed that the risk for

uterine cancer stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, *it is important to take the lowest dose that works and to take it only as long as you need it*. Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (see OTHER INFORMATION, below).

If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.

Cancer of the breast. The majority of studies have shown no association between the usual doses used for estrogen replacement therapy and breast cancer. Some studies have suggested a possible increased incidence of breast cancer in women taking estrogens for prolonged periods of time, especially in excess of 10 years if higher doses are used.

Regular breast examinations by a health professional, and monthly self-examinations, are recommended for women receiving estrogen therapy, as they are for all women.

Gallbladder disease. Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

Abnormal blood clotting. Taking estrogens may increase the risk of blood clots. These clots can cause a stroke, heart attack, or pulmonary embolus, any of which may cause death or long term serious disability.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Headache.
- Nausea and vomiting.
- Breast tenderness or enlargement.
- Enlargement of benign tumors ("fibroids") of the uterus.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face. Skin irritation, redness, or rash may occur at the site of application.

In Postmarketing experience, although a causal relationship with Vivelle has not been established, isolated reports of anaphylaxis as well as rare reports of elevated liver function tests have been received.

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:

See your doctor regularly. While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had

breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

Reassess your need for estrogens. You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

Be alert for signs of trouble. Report these or any other unusual side effects to your doctor immediately:

- Abnormal bleeding from the vagina.
- Pains in the calves or chest, sudden shortness of breath, or coughing blood (indicating possible clots in the legs, heart, or lungs).
- Severe headache, dizziness, faintness, or changes in vision (indicating possible clots in the brain or eye).
- Breast lumps.
- Yellowing of the skin or eyes.
- Pain, swelling, or tenderness in the abdomen.
- Skin irritation, redness, or rash.

OTHER INFORMATION

If your uterus has not been removed, your doctor may choose to prescribe a progestin, a different hormonal drug to be used in association with estrogen treatment. Progestins lower the risk of developing endometrial hyperplasia, a possible precancerous condition of the uterine lining, which may occur while using estrogen. There are possible additional risks that may be associated with the inclusion of a progestin in estrogen treatment. The possible risks include unfavorable effects on blood fats and sugars, as well as a possible further increase in breast cancer risk that may be associated with long-term estrogen use.

Some research has suggested that estrogen taken *without progestins* may protect women against developing heart disease. However, this effect of estrogen is not certain.

You are cautioned to discuss very carefully with your doctor or healthcare provider all the possible risks and benefits of long-term estrogen and progestin treatment, as they affect you personally.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

Keep this and all drugs out of the reach of children. In case of overdose, remove the system and call your doctor, hospital, or poison control center immediately.

This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling.

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