AFFIDAVIT

State of Maryland, Montgomery County

I, Marlene S. Bobka, under oath, hereby depose and state as follows:

1. I am the president of F.O.I., Inc. d/b/a FOI Services, Inc. ("FOI Services").

2. FOI Services is a privately-held corporation organized and operating under the laws of the State of Maryland, with its principal mailing address at 23219 Stringtown Road, Suite 240, Clarksburg, MD Maryland 20871, U.S.A.

3. FOI Services specializes in United States Food & Drug Administration ("FDA") information and maintains a private library of over 150,000 FDA documents obtained under the Freedom of Information Act ("FOIA") in all categories of products regulated by FDA, including drugs, biologics, veterinary products, foods and medical devices. These documents are sold individually; the copies we maintain and sell are faithful reproductions of the original documents supplied to us by FDA and, except for cover sheets, are not altered in any way. Many U.S. courts have accepted our documents as true copies of official FDA documents.

4. FOI Document # 5236149B (attached as Exhibit A) presents 24 pages of labeling documentation, and is a faithful reproduction of the labeling section originally provided as pages 10 -33 in the full releasable approval package of 211 provided by FDA in our Document # 5210475A. Document 5210475A was received from FDA as publicly available, incorporated into the FOI Services publicly available files, and was subsequently provided by FOI Services to a third party at least as early as 04/14/2006.

5. The record attached as Exhibit A was kept in the course of our regularly conducted business activity. Making the record was a regular practice of my job duties and our business activities.

6. I hereby declare that all statements made herein of my own knowledge are true and correct. I further declare that all of my statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Marlene S. Bobka

August 9, 2017

Date

SUBSCRIBED AND SWORN before me on

Notary Public

My commission expires: May, 03 2021

YESENIA SANCHEZ BUSTOS
NOTARY PUBLIC
MONTGOMERY COUNTY
MARYLAND
MY COMMISSION EXPIRES MAY 03, 2021

EXHIBIT A

foi

5236149

B

5236149 B

Vivelle-DOT (Novartis) 05/03/2002 Supplemental Approval [Label Revisions]: S12, S14, S15 Approvable Letter; Final Labeling; Approval Letter

This document was provided by: **FOI Services, Inc**
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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
20-538/S-015

Trade Name: Vivelle-Dot

Generic Name: estradiol transdermal system

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: May 3, 2002

Indications: Provides for the prevention of postmenopausal osteoporosis indication in at-risk patients for the .025 mg/day strengths.

5210475A

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-538/S-015

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Reviews / Information Included in this NDA Review.	
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Approvable Letter	X
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EA/FONSI	
Pharmacology Review(s)	X
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-538/S-015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-538/S-012, S-014, S-015

APPROVAL LETTER

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to your supplemental new drug applications dated March 1, 2002, received March 4, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivelle-Dot® (estradiol transdermal system).

We acknowledge receipt of your submission dated April 24, 2002. Your submission of March 1, 2002, constituted a complete response to our November 19, 2001 action letter.

These supplemental new drug applications propose changes for the use of Vivelle-Dot® as follows:

1. Revised labeling to incorporate safety information requested by the Agency in a letter dated August 10, 2000, (S-012),

2. Removal of the restrictive language, regarding vasomotor symptoms associated with the menopause, that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy and revision of the Clinical Pharmacology section of the Package Insert to be consistent with the FDA draft labeling guidance (S-014), and

3. Addition of the prevention of postmenopausal osteoporosis indication in at-risk patients for the .025 mg/day strength (S-015).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert).

Please submit the copies of final printed labeling (FPL) electronically to the application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-538/S-012, S-014, S-015." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

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

Enclosure

Appears This Way
On Original

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

/s/

Dena Hixon
5/3/02 03:11:15 PM
for Daniel Shames, MD

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On Original

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-538/S-015

APPROVED LABELING

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Approved Labeling

This supplemental application is not being approved during the first review cycle. An approved label has not been achieved.

NOVARTIS

T2000-56/T2000-57
89001003

Vivelle-Dot®
(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.

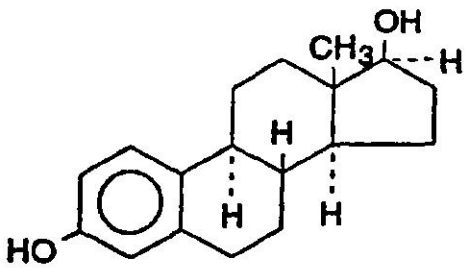
DESCRIPTION

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

Five dosage strengths of Vivelle-Dot are available to provide nominal *in vivo* delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5, 3.75, 5.0, 7.5, or 10.0 cm^2 and contains 0.39, 0.585, 0.78, 1.17, or 1.56 mg of estradiol USP, respectively. The composition of the systems per unit area is identical.

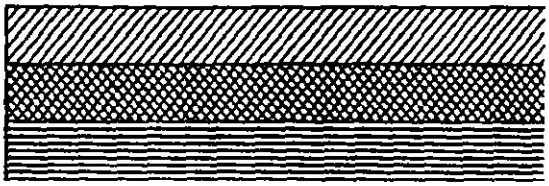
Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5 (10)-triene-3,17ß-diol.

The structural formula is



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

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



The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.

CLINICAL PHARMACOLOGY

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

Pharmacokinetics

The skin metabolizes estradiol only to a small extent. In contrast, orally administered estradiol is rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels of estrone than estradiol. Therefore, transdermal administration produces therapeutic plasma levels of estradiol with lower circulating levels of estrone and estrone conjugates and requires smaller total doses than does oral therapy.

Absorption

In a multiple-dose study consisting of three consecutive system applications of the original formulation [Vivelle® (estradiol transdermal system)] which was conducted in 17 healthy, postmenopausal women, blood levels of estradiol and estrone were compared following application of these units to sites on the abdomen and buttocks in a crossover fashion. Systems that deliver nominal estradiol doses of approximately 0.0375 mg/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

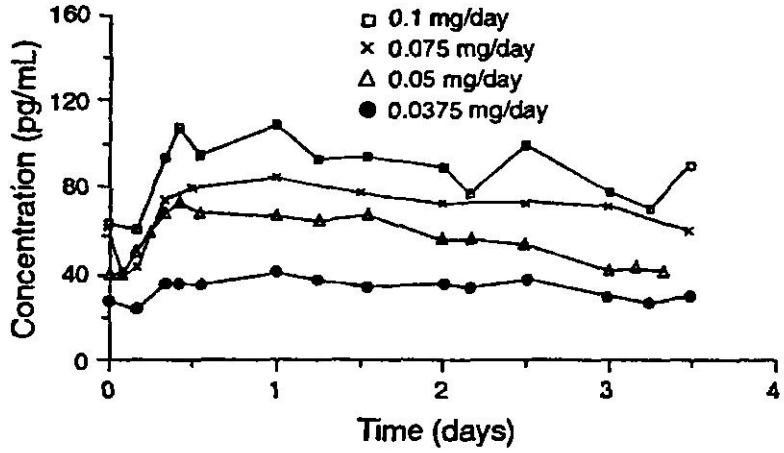
61 pg/mL for the buttocks. While plasma concentrations of estradiol and estrone remained slightly above baseline at 12 hours following removal of the systems in this study, results from another study show these levels to return to baseline values within 24 hours following removal of the systems.

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

Figure 1

Steady-State Estradiol Plasma Concentrations for Systems Applied to the Abdomen

Nonbaseline-corrected levels



The corresponding pharmacokinetic parameters are summarized in the table below.

Table 1.

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

Nonbaseline-corrected data*

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

*Mean baseline estradiol concentration = 11.7 pg/mL
†Peak plasma concentration
‡Average plasma concentration
§Minimum plasma concentration at 84 hr
#Measured over 80 hr
¶Applied to the buttocks

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

Distribution

No specific investigation of the tissue distribution of estradiol absorbed from Vivelle in humans has been conducted. The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

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

Excretion

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

Special Populations

Vivelle-Dot was investigated in postmenopausal women. No pharmacokinetic studies were conducted in other special populations.

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, phenytoin, carbamazepine, rifampin and dexamethasone 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 cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Adhesion

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

Clinical Studies

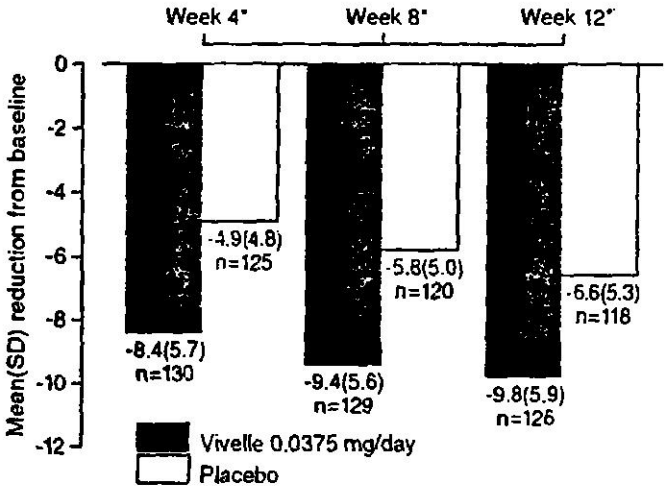
Effects on vasomotor symptoms

In a pharmacokinetic study, Vivelle-Dot was shown to be bioequivalent to Vivelle. In two controlled clinical trials with Vivelle, of 356 subjects, the 0.075 and 0.1 mg doses were superior to placebo in relieving vasomotor symptoms at Week 4, and maintained efficacy through Weeks 8 and 12 of treatment. The 0.0375 and 0.05 mg doses, however, did not differ from placebo until approximately Week 6.

Therefore, an additional 12-week placebo-controlled study in 255 patients was performed with Vivelle to establish the efficacy of the lowest dose of 0.0375 mg. The baseline mean daily number of hot flushes in these 255 patients was 11.5. Results at Weeks 4, 8, and 12 of treatment are shown in 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

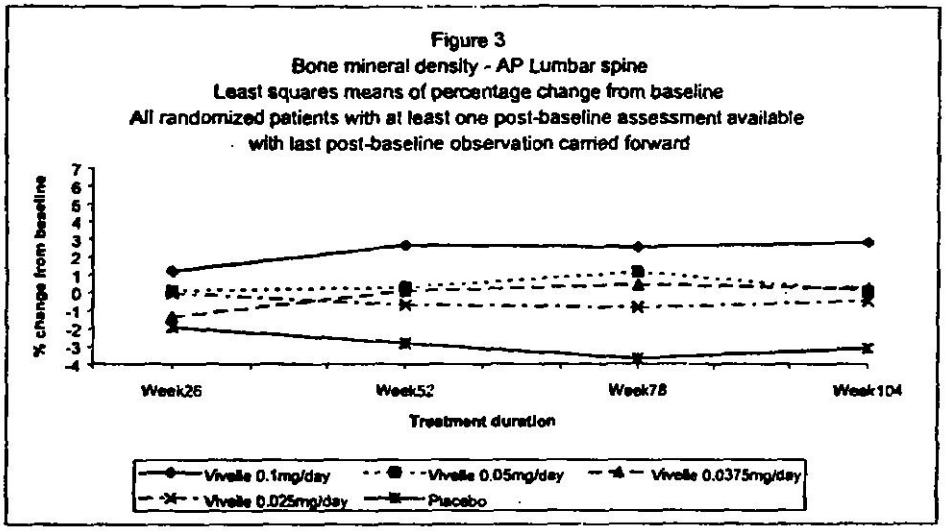
The 0.0375 mg dose was superior to placebo in reducing both the frequency and severity of vasomotor symptoms at Week 4 and maintained efficacy through Weeks 8 and 12 of treatment. All doses of Vivelle (0.0375 mg, 0.05 mg, 0.075 mg, and 0.1 mg) are effective for the control of vasomotor symptoms.

Effects on bone mineral density

Efficacy and safety of Vivelle in the prevention of postmenopausal osteoporosis have been studied in a 2-year double-blind, randomized, placebo-controlled, parallel group study. A total of 261 hysterectomized (161) and non-hysterectomized (100), surgically or naturally menopausal women (within 5 years of menopause), with no evidence of osteoporosis (lumbar spine bone mineral density within 2 standard deviations of average peak bone mass, i.e., ≥ 0.827 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.

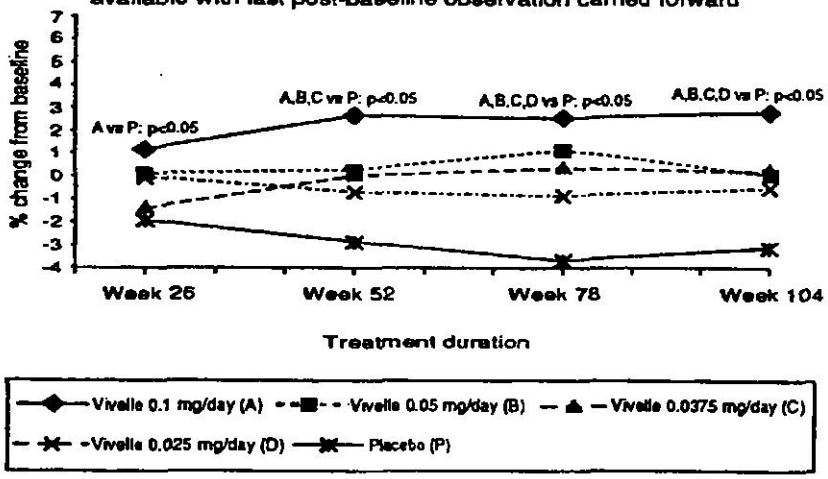
The study population comprised naturally (82%) or surgically (18%) menopausal, hysterectomized (61%) or nonhysterectomized (39%) women with a mean age of 52.0 years (range 27 to 62 years); the mean

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.)

Figure 4
Bone mineral density - Femoral neck
Least squares means of percentage change from baseline
All randomized patients with at least one post-baseline assessment available with last post-baseline observation carried forward



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

INDICATIONS AND USAGE

Vivelle-Dot is indicated in:

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.
4. Prevention of postmenopausal osteoporosis. Estrogen replacement therapy reduces bone resorption and retards postmenopausal bone loss. When estrogen therapy is discontinued, bone mass declines at a rate comparable to that of the immediate postmenopausal period.

   The mainstays of prevention of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake and, when indicated, estrogen. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. The average calcium intake in the USA is 400-600 mg/day. 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.

   Early menopause is one of the strongest predictors for the development of osteoporosis. Other factors associated with osteoporosis include genetic factors (small build, family history), lifestyle

(cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight and dietary calcium intake).

CONTRAINDICATIONS

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 deep vein thrombosis/pulmonary embolism or a history of these conditions.
6. Known hypersensitivity to any of the components of Vivelle-Dot

WARNINGS

1. **Induction of Malignant Neoplasms.**

   a. ***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.

   b. ***Breast cancer.***

   While some epidemiologic studies suggest a very modest increase in breast cancer risk for estrogen alone users versus non-users, other studies have not shown any increased risk. The addition of progestin to estrogen may increase the risk for breast cancer over that noted in non-hormone users more significantly (by about 24 to 40%), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials.

   Women without a uterus who require hormone replacement should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. Women with a uterus who are candidates for short-term combination estrogen/progestin therapy (for relief of vasomotor symptoms) are not felt to be at a substantially increased risk for breast cancer. Women with a uterus who are candidates for long-term use of estrogen/progestin therapy should be advised of potential benefits and risks (including the potential for an increased risk of breast cancer).

   All women should receive yearly breast exams by a healthcare 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.

2. **Thromboembolic Disorders.**

The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) using estrogen replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, estrogen replacement therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

Venous thromboembolism. Several epidemiologic studies have found an increased risk of thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2 to 3 cases per 10,000 women per year.

Cerebrovascular disease. Embolic cerebrovascular events have been reported in postmenopausal women receiving estrogens.

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.

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.

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 have reported a lower 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 in estrogen replacement regimens. These include adverse effects on lipoprotein metabolism (e.g., lowering HDL and raising LDL) and impairment of glucose tolerance. The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects.

2. ***Cardiovascular risk.*** The effects of estrogen replacement on the risk of cardiovascular disease have not been adequately studied. However, data from the Heart and Estrogen/Progestin Replacement Study

(HERS), a controlled clinical trial of secondary prevention of 2,763 postmenopausal women with documented heart disease, demonstrated no benefit. During an average follow-up of 4.1 years, treatment with oral conjugated estrogen plus medroxyprogesterone acetate did not reduce the overall rate of coronary heart disease (CHD) events in post-menopausal women with established coronary disease. There were more CHD events in the hormone treated group than in the placebo group in year 1, but fewer events in years 3 through 5.

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

4. ***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...

5. ***Impaired liver function.*** Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

6. ***Hypothroidism.*** 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.

7. ***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.

8. ***Exacerbation of endometriosis.*** Endometriosis may be exacerbated with administration of estrogen therapy.

9. ***Hypocalcemia.*** Estrogens should be used with caution in individuals with severe hypocalcemia.

B. **Patient Information .** See text of Patient Information after the **HOW SUPPLIED** section.

C. **Laboratory Tests.** Estrogen administration should be guided by clinical response at the lowest dose for the treatment of vasomotor symptoms and vulvar and vaginal atrophy. Laboratory parameters may be useful in guiding dosage for prevention of osteoporosis (bone mineral density) and the treatment of hypoestrogenism due to hypogonadism, castration and primary ovarian failure.

D. **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 triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

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 **CONTRAINDICATIONS.**

F. **Pregnancy Category X.** Vivelle-Dot should not be used during pregnancy. See CONTRAINDICATIONS. **Nursing Mothers.** The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Vivelle-Dot is not indicated for the prevention of postpartum breast engorgement.

G. **Pediatric Use.** Estrogen replacement 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 timeperiod 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 gynecomastia. See **INDICATIONS** and **DOSAGE AND ADMINISTRATION** sections.

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

ADVERSE REACTIONS

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.

See **WARNINGS** regarding induction of malignant neoplasms, thromboembolic disorders, gallbladder disease, and hypercalcemia; see **PRECAUTIONS** regarding cardiovascular risk and elevated blood pressure.

The following adverse events have been reported with Vivelle-Dot therapy:

Table 2. Summary of Most Frequently Reported Adverse Experiences/Medical Events Regardless of Relationship Reported at a Frequency ≥ 2%

	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 (%)
Ear and labyrinth disorders	0	0	4 (3.9)	3 (6.5)	2 (1.5)	5 (3.2)
Ear pain	0	0	3 (2.9)	0	0	0
Gastrointestinal disorders	15 (31.9)	43 (33.1)	27 (26.2)	9 (19.6)	27 (20.5)	36 (22.9)
Abdominal distension	0	5 (3.8)	3 (2.9)	0	2 (1.5)	2 (1.3)
Abdominal pain NOS*	0	5 (3.8)	2 (1.9)	0	5 (3.8)	4 (2.5)
Abdominal pain upper	0	4 (3.1)	0	0	0	0
Constipation	2 (4.3)	5 (3.8)	4 (3.9)	3 (6.5)	2 (1.5)	4 (2.5)
Diarrhoea NOS*	2 (4.3)	6 (4.6)	2 (1.9)	0	3 (2.3)	2 (1.3)
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)
Toothache	0	3 (2.3)	4 (3.9)	0	2 (1.5)	5 (3.2)
Vomiting NOS*	0	2 (1.5)	0	0	3 (2.3)	2 (1.3)
General disorders and administration site conditions	12 (25.5)	27 (20.8)	22 (21.4)	9 (19.6)	27 (20.5)	32 (20.4)
Application site erythema	0	3 (2.3)	3 (2.9)	0	2 (1.5)	5 (3.2)
Application site irritation	0	0	2 (1.9)	0	4 (3.0)	0
Chest pain	0	0	0	2 (4.3)	2 (1.5)	3 (1.9)
Fatigue	2 (4.3)	0	2 (1.9)	0	3 (2.3)	3 (1.9)
Influenza like illness	3 (6.4)	6 (4.6)	8 (7.8)	0	3 (2.3)	10 (6.4)
Oedema peripheral	2 (4.3)	2 (1.5)	3 (2.9)	0	2 (1.5)	0
Pain NOS*	0	8 (6.2)	0	2 (4.3)	7 (5.3)	7 (4.5)
Immune system disorders	2 (4.3)	7 (5.4)	5 (4.9)	1 (2.2)	5 (3.8)	8 (5.1)
Hypersensitivity NOS*	0	5 (3.8)	4 (3.9)	0	3 (2.3)	5 (3.2)
Infections and infestations	19 (40.4)	53 (40.8)	56 (54.4)	18 (39.1)	47 (35.6)	72 (45.9)
Bladder infection NOS*	0	0	2 (1.9)	2 (4.3)	0	3 (1.9)
Bronchitis NOS*	2 (4.3)	3 (2.3)	0	0	3 (2.3)	6 (3.8)
Candidal infection NOS*	2 (4.3)	3 (2.3)	0	0	2 (1.5)	0
Ear infection NOS*	0	0	3 (2.9)	0	0	5 (3.2)

Fungal infection NOS*	0	4 (3.1)	4 (3.9)	0	0	2 (1.3)
Herpes simplex	2 (4.3)	0	0	0	0	0
Influenza	4 (8.5)	4 (3.1)	6 (5.8)	0	10 (7.6)	14 (8.9)
Nasopharyngitis	3 (6.4)	16 (12.3)	10 (9.7)	9 (19.6)	11 (8.3)	24 (15.3)
Pharyngitis NOS*	0	3 (2.3)	0	0	0	0
Pleural infection NOS*	2 (4.3)	0	0	0	0	0
Sinusitis NOS*	4 (8.5)	17 (13.1)	13 (12.6)	3 (6.5)	7 (5.3)	16 (10.2)
Tooth abscess	0	3 (2.3)	0	0	0	3 (1.9)
Upper respiratory tract infection NOS*	3 (6.4)	8 (6.2)	11 (10.7)	4 (8.7)	6 (4.5)	9 (5.7)
Urinary tract infection NOS*	0	4 (3.1)	3 (2.9)	2 (4.3)	0	5 (3.2)
Vaginitis	0	0	2 (1.9)	0	4 (3.0)	0
Vaginosis fungal NOS*	0	2 (1.5)	5 (4.9)	0	2 (1.5)	0
Injury, poisoning and procedural complications	7 (14.9)	10 (7.7)	4 (3.9)	2 (4.3)	8 (6.1)	16 (10.2)
Arthropod bite	2 (4.3)	0	0	0	0	0
Joint sprain	2 (4.3)	2 (1.5)	0	0	0	5 (3.2)
Muscle strain	0	2 (1.5)	2 (1.9)	2 (4.3)	0	4 (2.5)
Investigations	5 (10.6)	8 (6.2)	3 (2.9)	3 (6.5)	4 (3.0)	4 (2.5)
Weight increased	4 (8.5)	5 (3.8)	2 (1.9)	2 (4.3)	0	3 (1.9)
Metabolism and nutrition disorders	1 (2.1)	5 (3.8)	2 (1.9)	3 (6.5)	5 (3.8)	4 (2.5)
Fluid retention	0	4 (3.1)	0	3 (6.5)	4 (3.0)	3 (1.9)
Musculoskeletal and connective tissue disorders	12 (25.5)	37 (28.5)	33 (32.0)	8 (17.4)	34 (25.8)	39 (24.8)
Arthralgia	0	11 (8.5)	4 (3.9)	2 (4.3)	5 (3.8)	9 (5.7)
Arthritis NOS*	0	4 (3.1)	0	0	3 (2.3)	2 (1.3)
Back pain	4 (8.5)	10 (7.7)	9 (8.7)	4 (8.7)	14 (10.6)	10 (6.4)
Muscle cramps	0	0	0	0	0	6 (3.8)
Muscle spasms	0	3 (2.3)	2 (1.9)	0	0	0
Myalgia	0	5 (3.8)	4 (3.9)	0	0	5 (3.2)
Neck pain	3 (6.4)	4 (3.1)	4 (3.9)	0	6 (4.5)	2 (1.3)
Osteoarthritis NOS*	2 (4.3)	0	0	0	0	0
Pain in limb	0	10 (7.7)	7 (6.8)	2 (4.3)	6 (4.5)	9 (5.7)
Peripheral swelling	0	0	4 (3.9)	0	0	0
Nervous system disorders	9 (19.1)	50 (38.5)	40 (38.8)	24 (52.2)	39 (29.5)	48 (30.6)
Carpal tunnel syndrome	0	0	3 (2.9)	0	0	0
Dizziness (excl vertigo)	0	4 (3.1)	0	0	0	4 (2.5)
Headache NOS*	7 (14.9)	35 (26.9)	32 (31.1)	23 (50.0)	34 (25.8)	37 (23.6)
Hypoaesthesia	2 (4.3)	0	0	0	0	0
Migraine NOS*	0	6 (4.6)	2 (1.9)	0	2 (1.5)	3 (1.9)
Sinus headache	0	12 (9.2)	5 (4.9)	5 (10.9)	2 (1.5)	8 (5.1)
Tension headaches	0	0	2 (1.9)	0	0	4 (2.5)
Psychiatric disorders	11 (23.4)	18 (13.8)	15 (14.6)	6 (13.0)	9 (6.8)	18 (11.5)

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)
Emotional disturbance NOS*	0	2 (1.5)	3 (2.9)	0	2 (1.5)	0
Insomnia	3 (6.4)	6 (4.6)	4 (3.9)	2 (4.3)	2 (1.5)	9 (5.7)
Reproductive system and breast disorders	15 (31.9)	27 (20.8)	21 (20.4)	8 (17.4)	35 (26.5)	15 (9.6)
Breast pain	0	3 (2.3)	3 (2.9)	0	0	0
Breast tenderness	8 (17.0)	10 (7.7)	8 (7.8)	3 (6.5)	17 (12.9)	0
Dysmenorrhoea	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)
Vaginal discharge	2 (4.3)	3 (2.3)	3 (2.9)	0	2 (1.5)	0
Vaginal haemorrhage	0	0	0	2 (4.3)	0	0
Respiratory, thoracic and mediastinal disorders	2 (4.3)	21 (16.2)	14 (13.6)	7 (15.2)	15 (11.4)	25 (15.9)
Cough	0	2 (1.5)	3 (2.9)	0	3 (2.3)	6 (3.8)
Nasal congestion	0	6 (4.6)	2 (1.9)	2 (4.3)	4 (3.0)	5 (3.2)
Pharyngolaryngeal pain	0	6 (4.6)	2 (1.9)	0	6 (4.5)	6 (3.8)
Rhinitis NOS*	0	4 (3.1)	0	0	0	0
Sinus congestion	0	4 (3.1)	3 (2.9)	3 (6.5)	6 (4.5)	7 (4.5)
Skin and subcutaneous tissue disorders	8 (17.0)	16 (12.3)	10 (9.7)	2 (4.3)	16 (12.1)	19 (12.1)
Acne NOS*	0	3 (2.3)	0	0	3 (2.3)	0
Erythema	0	0	0	0	0	4 (2.5)
Pruritus NOS*	0	5 (3.8)	0	0	0	2 (1.3)
Rash NOS*	2 (4.3)	5 (3.8)	5 (4.9)	2 (4.3)	4 (3.0)	4 (2.5)
Urticaria NOS*	0	0	0	0	0	5 (3.2)
Vascular disorders	6 (12.8)	4 (3.1)	5 (4.9)	0	4 (3.0)	11 (7.0)
Hot flushes NOS*	3 (6.4)	0	3 (2.9)	0	0	6 (3.8)
Hypertension NOS*	2 (4.3)	0	3 (2.9)	0	0	2 (1.3)

†Represents milligrams of estradiol delivered daily by each system
* NOS represents not otherwise specified
** NEC represents not elsewhere classified

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 Vivelle-Dot should be placed on a clean, dry area of the abdomen. *Vivelle-Dot should not be applied to the breasts.* Vivelle-Dot should be replaced twice weekly. The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the event that a system should fall off the same system may be reapplied. If the same system cannot be reapplied a new system should be applied to another location. In either case, the original treatment schedule should be continued.

Initiation of Therapy

For treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, start therapy with Vivelle-Dot 0.0375 mg/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 Vivelle-Dot may be initiated at once. In women who are currently taking oral estrogens, treatment with Vivelle-Dot should be initiated 1 week after withdrawal of oral hormone replacement therapy, or sooner if menopausal symptoms reappear in less than 1 week.

For the prevention of 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.

Therapeutic Regimen

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

HOW SUPPLIED

Vivelle-Dot® (estradiol transdermal system), 0.025 mg/day - each 2.5 cm^2 system contains 0.39 mg of estradiol USP for nominal* delivery of 0.025 mg of estradiol per day. Patient Calendar Pack of 8 Systems ..... NDC 0078-0365-42
Carton of 3 Patient Calendar Packs of 8 Systems ..... NDC 0078-0365-45

Vivelle-Dot® (estradiol transdermal system), 0.0375 mg/day - each 3.75 cm^2 system contains 0.585 mg of estradiol USP for nominal* delivery of 0.0375 mg of estradiol per day. Patient Calendar Pack of 8 Systems ..... NDC 0078-0343-42
Carton of 3 Patient Calendar Packs of 8 Systems ..... NDC 0078-0343-45

Vivelle-Dot® (estradiol transdermal system), 0.05 mg/day - each 5.0 cm^2 system contains 0.78 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.
Patient Calendar Pack of 8 Systems ..... NDC 0078-0344-42
Carton of 3 Patient Calendar Packs of 8 Systems ..... NDC 0078-0344-45

Vivelle-Dot® (estradiol transdermal system), 0.075 mg/day - each 7.5 cm^2 system contains 1.17 mg of estradiol USP for nominal* delivery of 0.075 mg of estradiol per day.
Patient Calendar Pack of 8 Systems ..... NDC 0078-0345-42
Carton of 3 Patient Calendar Packs of 8 Systems ..... NDC 0078-0345-45

Vivelle-Dot® (estradiol transdermal system), 0.1 mg/day - each 10.0 cm^2 system contains 1.56 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.
Patient Calendar Pack of 8 Systems ..... NDC 0078-0346-42
Carton of 3 Patient Calendar Packs of 8 Systems ..... NDC 0078-0346-45

*See DESCRIPTION.

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

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

REV: April 2002 T2000-56

Information for the Patient T2000-57
Vivelle-Dot®
(estradiol transdermal system)

Rx only

The Vivelle-Dot patch that your healthcare 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-Dot. Vivelle-Dot 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-DOT ?

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS.

If you use any medicines containing estrogen, it is important to visit your doctor or healthcare provider regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor or healthcare provider should check any unusual vaginal bleeding to find out the cause. Women who do not have a uterus have almost no risk of endometrial cancer.

INTRODUCTION

What is Vivelle-Dot?

Vivelle-Dot (pronounced vi-Vel-Dot) is a patch that contains the estrogen hormone estradiol. When applied to the skin as directed below, Vivelle-Dot releases estrogen through the skin into the bloodstream.

VIVELLE-DOT IS APPROVED FOR THE FOLLOWING USES :

- **To reduce moderate or severe menopausal symptoms.**

Estrogens are hormones made by a women's ovaries. When a women is between ages 45 and 55, the ovaries normally stop making estrogens. This drop in body estrogen levels causes the "Change in life" or menopause (the end of monthly periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause."

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild and in others they can be severe. Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Many women have only mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their

bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.

- **To treat itching, burning and dryness in and around the vagina associated with menopause**
- **To treat certain conditions in which a young women's ovaries do not produce enough estrogens naturally.**
- **To help reduce your chances of getting osteoporosis (thin weak bones)**

Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. Women who have menopause at an earlier age either naturally or because their ovaries were removed during an operation are more likely to develop osteoporosis than women whose menopause happens later in life. Women who are more likely to develop osteoporosis often have one or more of the following characteristics: slim body frame, cigarette smoker, or family history of osteoporosis in a mother, sister or aunt.

Vivelle-Dot may be used as part of a program which includes weight-bearing exercise like walking and running and taking calcium and Vitamin D supplements to reduce your chances of getting osteoporosis. Before you change your exercise habits or calcium or Vitamin D intake or, it is important to discuss these lifestyle changes with your healthcare provider to find out if they are safe for you.. You and your healthcare provider have agreed that you should take Vivelle-Dot to reduce your chances of getting osteoporosis. You may need to take Vivelle-Dot for a long period of time. Before you make any change in your use of Vivelle-Dot, talk with your healthcare provider.

WHO SHOULD NOT USE VIVELLE-DOT

Vivelle-Dot should not be used:

- **During pregnancy .**

  If you think you may be pregnant, do not use Vivelle-Dot. Using Vivelle-Dot while you are pregnant may cause harm to your unborn child. Do not use Vivelle-Dot to prevent miscarriage.

- **If you have unusual vaginal bleeding which has not been evaluated by your healthcare provider.**

  Unusual vaginal bleeding can be a warning sign of serious conditions, including cancer of the uterus, especially if it happens after menopause. Your healthcare provider must find out the cause of the bleeding so that he or she can recommend the proper treatment.

- **If you have or have had cancer.**

  Estrogens increase the risk of certain types of cancer, including cancer of the breast or uterus. If you have or have had cancer, talk to your healthcare provider about the use of Vivelle-Dot.

- **If you have any circulation problems (blood clots or problems with blood flow).**

  Talk with your healthcare provider about your condition. Do not use Vivelle-Dot if you have blood clots or have had them in the past.

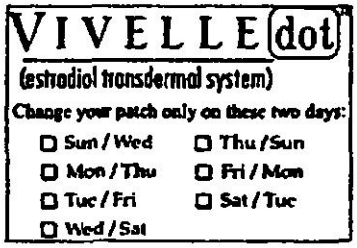
- **After childbirth or when breastfeeding a baby.**

Do not use Vivelle-Dot to try to stop the breasts from filling with milk after a baby is born.

- **If you are allergic to Vivelle-Dot or any of the ingredients in it.** Your healthcare provider can give you a list of the ingredients in Vivelle-Dot.

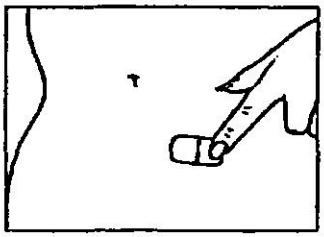
Application Instructions for Vivelle-Dot (estradiol transdermal system)

1. DETERMINE YOUR SCHEDULE FOR YOUR TWICE-A-WEEK APPLICATION



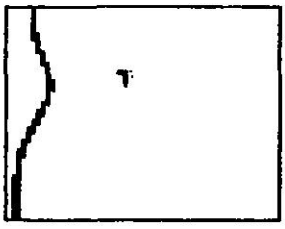
- Decide upon which two days you will change your patch.
- Your Vivelle-Dot individual carton contains a calendar card printed on its inner flap. Mark the two-day schedule you plan to follow on your carton's inner flap.
- **BE CONSISTENT.**
- If you forget to change your patch on the correct date, apply a new one as soon as you remember.
- No matter what day this happens, stick to the schedule you have marked on the inner flap of your carton (your calendar card).

2. WHERE TO APPLY THE VIVELLE-DOT



- Apply patch to lower abdomen, below the waistline. Avoid the waistline, since clothing may cause the patch to rub off.
- **DO NOT APPLY PATCH TO BREASTS.**
- When changing your patch, based on your twice-a-week schedule, apply your new patch to a different site. Do not apply a new patch to that same area for at least one week.

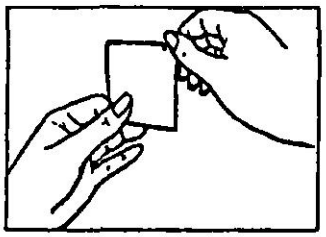
3. BEFORE YOU APPLY THE VIVELLE-DOT



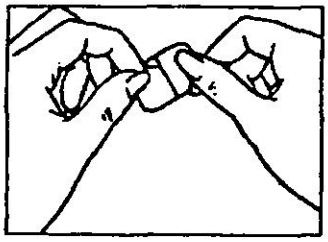
Make sure your skin is:

- Clean (freshly washed), dry and cool.
- Free of any powder, oil, moisturizer or lotion.
- Free of cuts and/or irritations (rashes or other skin problems).

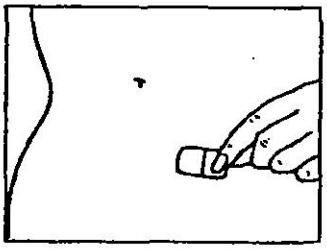
4. HOW TO APPLY THE VIVELLE-DOT



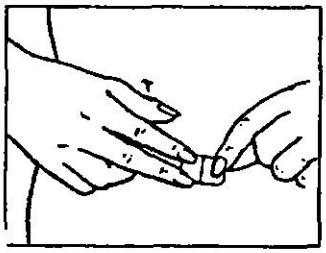
- Each patch is individually sealed in a protective pouch.
- Tear open the pouch at the tear notch (do not use scissors).
- Remove the patch.



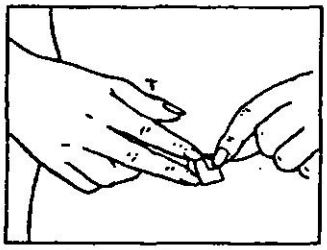
- **Apply the patch immediately after removing from pouch.**
- Holding the patch with the rigid protective liner facing you, remove **half** of the liner, which covers the sticky surface of the patch.



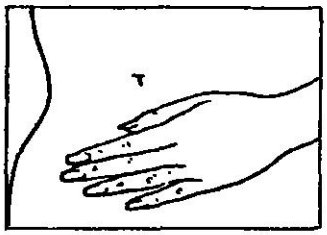
- **AVOID TOUCHING THE STICKY SIDE OF THE PATCH WITH YOUR FINGERS.**
- Using the other half of the rigid protective liner as a handle, apply the sticky side of the patch to the selected area of the abdomen.



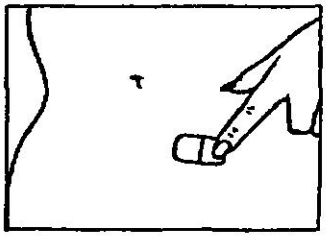
- Press the sticky side of the patch firmly into place.
- Smooth it down.
- While still holding the sticky side down, fold back the other half of the patch.



- Grasp an edge of the remaining protective liner and gently pull it off.
- **AVOID TOUCHING THE STICKY SIDE OF THE PATCH WITH YOUR FINGERS.**



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



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

PLEASE NOTE:

- Contact with water while bathing, swimming or showering will not affect the patch.

- In the event that a patch should fall off, **AVOID TOUCHING THE STICKY SIDE WITH YOUR FINGERS**. Put the same patch back on a different site, making sure to press the patch firmly into place for at least 10 seconds.
- Continue to follow your original twice-a-week schedule you have marked on the inner flap of your individual carton (your calendar card).
- If necessary, if the same patch cannot be reapplied, apply a new patch at another location but continue to follow your original schedule.

5. **HOW TO CHANGE AND DISCARD VIVELLE-DOT**

- When changing the patch, peel off the used patch slowly.
- Fold the used patch in half (sticky sides together) and discard appropriately, in the trash.
- **PLEASE KEEP OUT OF REACH OF CHILDREN.**
- If any adhesive residue remains on your skin after removing the patch, allow the area to dry for 15 minutes. Then, gently rub the area with oil or lotion to remove the adhesive from your skin.
- Keep in mind, **the new patch must be applied to a different area of your abdomen**. This area must be clean, dry, cool and free of powder, oil and/or lotion.

WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS OF VIVELLE-DOT?

Common side effects include:

- Headache.
- Nausea and vomiting.
- Breast tenderness or enlargement.
-
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- . Skin irritation, redness, or rash may occur at the site of application.
- Vaginal spotting or bleeding
-

Less common but serious effects include:

- **Cancer of the uterus.**
- **Cancer of the breast.**
- **Gallbladder disease.**
- **Abnormal blood clotting.**

These are some of the warning signs of serious effects:
Unusual vaginal bleeding.
Breast lumps.
Pains in your legs.
Severe headache and vomiting.
Dizziness and faintness.
Changes in vision or speech.

If you have any of these warning signs, or other unusual symptoms that concern you, call your healthcare provider right away.

WHAT CAN I DO TO LOWER MY CHANCES OF GETTING A SERIOUS SIDE EFFECT WITH VIVELLE-DOT?If you use Vivelle-Dot, you can reduce your risks by

Seeing your healthcare provider regularly.

While you are using Vivelle-Dot, it is important to visit your healthcare provider at least once a year for a check-up. If you develop vaginal bleeding while taking Vivelle-Dot, 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.

OTHER INFORMATION

Do not store above 25°C (77°F). Do not store outside of their pouches. Apply immediately upon removal from the protective pouch.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Vivelle-Dot for conditions for which it was not prescribed.

Do not give Vivelle-Dot to other people, even if they have the same symptoms you have. It may harm them.

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 summarizes the most important information about Vivelle-Dot. If you would like more information, talk to your healthcare provider. You can ask for information about Vivelle-Dot that is written for health professionals.

T2000-57

REV: April 2002 Printed in U.S.A. T2000-56/T2000-57
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Miami, FL 33186

Distributed by
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-538/S-015

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-538/S-012, S-014, S-015

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to your supplemental new drug applications dated November 13, 2000, received November 15, 2000, resubmitted November 6, 2001, received November 8, 2001 (S-012); January 18, 2001, received January 19, 2001, (S-014), and January 22, 2001, received January 23, 2001, (S-015) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivelle-Dot™ (estradiol transdermal system) 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day.

We acknowledge receipt of your submissions dated: October 10, November 6, 8, 13, 15 and 16 (2), 2001 (S-012), January 18, February 12, March 7, October 1, November 6 (2), 8, 13, 15 and 16(2), 2001 (S-014) and January 22, February 12, May 18 and 25, July 17, October 1 and 16, November 6, 8, 13, 15, and November 16 (2), 2001 (S-015).

These supplemental new drug applications propose changes for the use of Vivelle-Dot™ as follows:

1. Revised labeling to incorporate safety information requested by the Agency in a letter dated August 10, 2000, (S-012),

2. Removal of the restrictive language, regarding vasomotor symptoms associated with the menopause, that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy and revision of the Clinical Pharmacology section of the Package Insert to be consistent with the FDA draft labeling guidance (S-014), and

3. Addition of the prevention of postmenopausal osteoporosis indication in at-risk patients for the 0.025 mg/day strength (S-015).

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit draft labeling that incorporates the revisions in the enclosed Package Insert and Patient Information insert. Additions have been noted with underlining and deletions have been noted with ~~strikeouts.~~ Additional comments requiring response are in **14 pt bold face type**. A clean version copy has also been provided.

In addition, on the Physician Sample Box, the "Rx Only" statement should be moved to the main panel of the box.

Furthermore, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDAs by submitting all safety information you now have regarding your new drugs. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Revised labeling

46 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Daniel A. Shames
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