CombiPatch™

estradiol / norethindrone acetate transdermal system

NDA #20-870

5 Aug FDA Labeling Proposals to Package Insert

DESCRIPTION

CombiPatch™ estradiol/norethindrone acetate transdermal system, is an adhesive-based matrix transdermal patch designed to release both 17β-estradiol and norethindrone acetate (NETA), a progestational agent, continuously upon application to intact skin.

Two systems are available, providing the following delivery rates of estradiol and norethindrone acetate.

System Size	Estradiol (mg)	NETA[1] (mg)	Nominal Delivery Rate[2] (mg per day) Estradiol / NETA
9 sq cm round	0.62	2.7	0.05 / 0.14
16 sq cm round	0.51	4.8	0.05 / 0.25

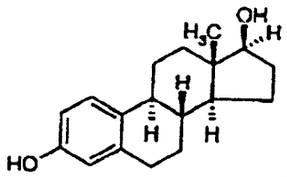
1 NETA = norethindrone acetate

2 Based on *in vivo/in vitro* flux data, delivery of both components per day via skin of average permeability (inter-individual variation in skin permeability is approximately 20%).

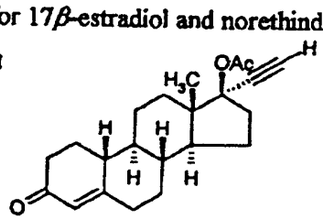
Estradiol USP (17β-estradiol) is a white to creamy white, odorless, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. The molecular weight of estradiol is 272.39 and the molecular formula is $C_{18}H_{24}O_2$.

Norethindrone acetate USP is a white to creamy white, odorless, crystalline powder, chemically described as 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate. The molecular weight of norethindrone acetate is 340.47 and the molecular formula is $C_{22}H_{28}O_3$.

The structural formulas for 17β-estradiol and norethindrone acetate are:

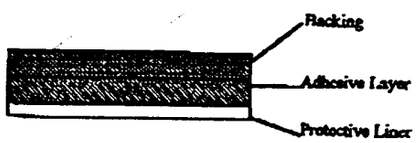


17β-Estradiol



Norethindrone Acetate

CombiPatch™ is an alcohol-free, adhesive-based matrix transdermal drug delivery system comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are a backing, an adhesive layer, and a protective liner. The adhesive matrix containing estradiol and norethindrone acetate is applied to a backing of polyester/ethylene vinyl acetate laminate film on one side and is protected on the other side by a transparent fluoropolymer-coated release liner. The transparent release liner must be removed before the system can be used. Each system is enclosed in a heat-sealed pouch.



CLINICAL PHARMACOLOGY

The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive: a silicone and acrylic-based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

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 in 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, lutcinizing 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.

Absorption: *Estradiol:* Estrogens used in hormone replacement therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. Administration of CombiPatch™ every 3 to 4 days in postmenopausal women produces average steady-state estradiol serum concentrations of 45 to 50 pg/mL, which are equivalent to the normal ranges observed at the early follicular phase in premenopausal women. These concentrations are achieved within 12 to 24 hours following CombiPatch™ application. Minimal fluctuations in serum estradiol concentrations are observed following CombiPatch™ application, indicating consistent hormone delivery over the application interval.

In one study, serum concentrations of estradiol were measured in 40 healthy, postmenopausal women throughout three consecutive CombiPatch™ applications to the abdomen (each dose was applied for three 3.5 day periods). The corresponding pharmacokinetic parameters are summarized in Table I below.

Table I. Mean (SD) Serum Estradiol and Estrone Concentrations (pg/mL) at Steady-State [Uncorrected for Baseline Levels]

System Size	Dose Estradiol / NETA (mg per day)	C_{max}	C_{min}	C_{ave}
Estradiol				
9 sq cm	0.05 / 0.14	71 (32)	27 (17)	45 (21)
16 sq cm	0.05 / 0.25	71 (30)	37 (17)	50 (21)
Estrone				
9 sq cm	0.05 / 0.14	72 (23)	49 (19)	54 (19)
16 sq cm	0.05 / 0.25	78 (22)	58 (22)	60 (18)

Norethindrone: Progestins used in hormone replacement therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. Norethindrone steady state concentrations are attained within 24 hours of application of the CombiPatch™ transdermal delivery systems. Minimal fluctuations in serum norethindrone concentrations are observed following CombiPatch™ treatment, indicating consistent hormone delivery over the application interval. Serum concentrations of norethindrone increase linearly with increasing doses of norethindrone acetate.

In one study, serum concentrations of norethindrone were measured in 40 healthy, postmenopausal women throughout three consecutive CombiPatch™ applications to the abdomen (each dose was applied for three 3.5 day periods). The corresponding pharmacokinetic parameters are summarized in Table II below.

Table II. Mean (SD) Serum Norethindrone Concentrations (pg/mL) at Steady-State

System Size	Dose Estradiol / NETA (mg per day)	C_{max}	C_{min}	C_{avg}
9 sq cm	0.05 / 0.14	617 (341)	386 (137)	489 (244)
16 sq cm	0.05 / 0.25	1060 (543)	686 (306)	840 (414)

Distribution: *Estradiol*: Estradiol circulates in the blood bound to sex hormone binding globulin (SHBG) and, to a lesser extent, albumin.

Norethindrone: In plasma, norethindrone is bound approximately 90% to SHBG and albumin.

Metabolism and Excretion: *Estradiol*: Transdermally delivered estradiol is metabolized only to a small extent by the skin and bypasses the first-pass effect seen with orally administered estrogen products. Therapeutic estradiol serum levels with lower circulating levels of estrone and estrone conjugates are achieved with smaller transdermal doses (daily and total) as compared to oral therapy, and more closely approximate premenopausal concentrations.

Estradiol has a short elimination half-life of approximately 2 to 3 hours; therefore, a rapid decline in serum levels is observed after the CombiPatch™ system is removed. Within 4 to 8 hours serum estradiol concentrations return to untreated, postmenopausal levels (<20 pg/mL).

Concentration data from Phase II and III studies indicate that the pharmacokinetics of estradiol did not change over time, suggesting no evidence of the accumulation of estradiol following extended patch wear periods (up to 1 year).

Norethindrone: Norethindrone acetate is hydrolyzed to the active moiety, norethindrone, in most tissues including skin and blood. Norethindrone is primarily metabolized in the liver; however, transdermal administration significantly decreases metabolism because hepatic first-pass effect is avoided.

The elimination half-life of norethindrone is reported to be 6 to 8 hours. Norethindrone serum concentrations diminish rapidly and are less than 50 pg/mL within 48 hours after removal of the CombiPatch™ transdermal delivery system.

Concentration data from Phase II and III studies indicate that the pharmacokinetics of norethindrone did not change over time, suggesting no evidence of the accumulation of norethindrone following extended patch wear periods (up to 1 year).

Adhesion: Averaging across six clinical trials lasting 3 months to one year, of 1287 patients treated, CombiPatch™ transdermal systems completely adhered to the skin nearly 90% of the time over the 3 to 4 day wear period. Less than 2% of the patients required reapplication or replacement of systems due to lifting or detachment. Only two patients (0.2%) discontinued therapy during clinical trials due to adhesion failure.

Special Populations: CombiPatch™ has been studied only in postmenopausal women.

CLINICAL STUDIES

In two clinical trials designed to assess the degree of relief of moderate-to-severe vasomotor symptoms in postmenopausal women (n=332), CombiPatch™ was administered for three 28-day cycles in *Continuous Combined* or *Continuous Sequential* treatment regimens versus placebo. In the *Continuous Combined* regimen, CombiPatch™ was applied throughout the three cycles, replacing the system twice weekly. In the *Continuous Sequential* regimen, an estradiol-only transdermal system (VIVELLE® 0.05 mg) was applied twice weekly during the first 14 days of a 28-day cycle; CombiPatch™ was applied for the remaining 14 days of the cycle and replaced twice weekly, as well. The mean number of hot flushes at baseline were 10 to 11 per day and 11 to 12 per day in the *Continuous Combined* and *Continuous Sequential* regimen trials, respectively. The mean number and intensity of daily hot flushes (intent-to-treat population) was significantly reduced from baseline to endpoint with either the *Continuous Combined* or *Continuous Sequential* administration of CombiPatch™ at all doses as compared to placebo (intent-to-treat population). [See tables below.]

Adjusted Mean Change in the Number of Hot Flushes and Daily Intensity of Hot Flushes per Day in CombiPatch™ *Continuous Combined* Transdermal Therapy

	CombiPatch™ Continuous Combined		Placebo
Adjusted Mean Change from Baseline[1]	0.05/0.14 mg per day[2] n = 57	0.05/0.25 mg per day[2] n = 52	n = 51
Number of Hot Flushes[3]	-9.3[5]	-8.9[5]	-6.2
Daily Intensity of Hot Flushes[3,4]	-4.6[5,6]	-5.0[5]	-2.8[7]

[1] Means were adjusted for imbalance among treatment groups and investigators (least squares mean from ANOVA).
[2] Represents the milligrams of estradiol/norethindrone acetate delivered daily by each system
[3] Population represents those patients who had baseline and endpoint observations.
[4] The intensity of hot flushes was evaluated on a scale of 0 to 9 (none = 0, mild = 1-3, moderate = 4-6, severe = 7-9).
[5] P value versus placebo = <0.001
[6] Total number of patients with available data is 56.
[7] Total number of patients with available data is 50.

Adjusted Mean Change in the Number of Hot Flushes and Daily Intensity of Hot Flushes per Day in CombiPatch™ *Continuous Sequential* Transdermal Therapy

Adjusted Mean Change from Baseline[1]	CombiPatch™ Continuous Sequential 0.05/0.14 mg per day[2] n = 54	CombiPatch™ Continuous Sequential 0.05/0.25 mg per day[2] n = 59	Placebo n = 53
Number of Hot Flushes[3]	-9.3[5]	-9.5[5]	-5.5
Daily Intensity of Hot Flushes[3,4]	-4.4[5]	-4.5[5]	-2.1

[1] Means were adjusted for imbalance among treatment groups and investigators (least squares mean from ANOVA).
[2] Represents the milligrams of estradiol/norethindrone acetate delivered daily by each system
[3] Population represents those patients who had baseline and endpoint observations.
[4] The intensity of hot flushes was evaluated on a scale of 0 to 9 (none = 0, mild = 1-3, moderate = 4-6, severe = 7-9).
[5] P value versus placebo = <0.001

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. Progestins counter the estrogenic effects by decreasing the number of nuclear estradiol receptors and suppressing epithelial DNA synthesis in endometrial tissue.

Clinical studies indicate that the addition of a progestin to an estrogen replacement regimen at least 12 days per cycle reduces the incidence of endometrial hyperplasia and the potential risk of adenocarcinoma in women with intact uteri. The addition of a progestin to an estrogen replacement regimen has not been shown to interfere with the efficacy of estrogen replacement therapy for its approved indications.

CombiPatch™ was effective in reducing the incidence of estrogen-induced endometrial hyperplasia after 1 year of therapy in two Phase II clinical trials. Nine hundred fifty-five (955) postmenopausal women (with intact uteri) were treated with (i) a continuous regimen of CombiPatch™ alone *(Continuous Combined* regimen), (ii) a sequential regimen with an estradiol-only (VIVELLE® 0.05 mg) transdermal system followed by a CombiPatch™ transdermal system (*Continuous Sequential* regimen), or (iii) continuous regimen with an estradiol-only transdermal system (VIVELLE® 0.05 mg). The incidence of endometrial hyperplasia (primary endpoint) was significantly less after 1 year of therapy with either CombiPatch™ regimen than with the estradiol-only transdermal system. The tables below summarize these results (intent-to-treat populations).

Incidence of Endometrial Hyperplasia in a *Continuous Combined* CombiPatch™ Regimen

	CombiPatch™ Continuous Combined 0.05 / 0.14 mg per day[1]	CombiPatch™ Continuous Combined 0.05 / 0.25 mg per day[1]	VIVELLE® Continuous 0.05 mg per day
No. of Patients with Biopsies[2]	123	98	103
No. (%) of Patients with Hyperplasia	1 (<1%)[3]	1 (1%)[3,4]	39 (38%)[5]

[1] Represents milligrams of estradiol / NETA delivered daily by each system
[2] Biopsy after 12 cycles of treatment or hyperplasia before cycle 12
[3] Comparison of continuous combined regimen versus estradiol-only patch was significant (p value <0.001).
[4] This patient had hyperplasia at baseline.
[5] One of 39 patients had hyperplasia in an endometrial polyp.

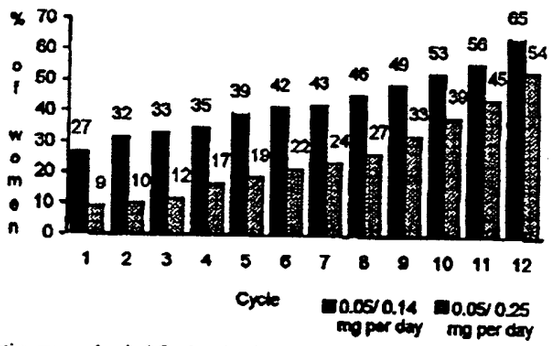
Incidence of Endometrial Hyperplasia in a *Continuous Sequential* CombiPatch™ Regimen

	CombiPatch™ Continuous Sequential		VIVELLE® Continuous
	0.05 / 0.14 mg per day[1]	0.05 / 0.25 mg per day[1]	0.05 mg per day
No. of Patients with Biopsies[2]	117	114	115
No. (%) of Patients with Hyperplasia	1 (<1%)[3,4]	1 (<1%)[3,5]	23 (20%)

[1] Represents milligrams of estradiol / NETA delivered daily by each system
[2] Biopsy after 12 cycles of treatment or hyperplasia before cycle 12
[3] Comparison of continuous sequential regimen versus estradiol-only patch was significant (p value < 0.001)
[4] This patient had hyperplasia at baseline
[5] This patient had hyperplasia in an endometrial polyp.

With the *Continuous Combined* regimen, of the women treated with CombiPatch™ and who completed the one year study, the incidence of cumulative amenorrhea (the absence of bleeding or spotting during a 28-day cycle and sustained to the end of the study) increased over time. The incidence of amenorrhea from cycle 10 through 12 was 53% and 39% for the CombiPatch™ 0.05/0.14 mg per day and CombiPatch™ 0.05/0.25 mg per day treatment groups, respectively. Women who experienced bleeding, usually characterized it as light (intensity of 1.3 on a scale of 1 to 4) with a duration of 4 and 6 days for the CombiPatch™ 0.05/0.14 mg per day and CombiPatch™ 0.05/0.25 mg per day treatment groups, respectively.

Incidence of Cumulative Amenorrhea*
in CombiPatch™ *Continuous Combined* Transdermal Therapy
by Cycle over a One-Year Period (Intent-to-Treat Population)



*Cumulative amenorrhea is defined as the absence of bleeding for the duration of a 28-day cycle and sustained to the end of the study.

Information Regarding Lipid Effects: The results of clinical trials conducted in a 90% Caucasian population at low risk for cardiovascular disease showed that compared to Vivelle (an estrogen-alone treatment), CombiPatch™ demonstrated significantly greater reductions in total cholesterol (TC) concentrations. Mean high density lipoprotein-cholesterol (HDL-C) values, however, decreased after one year of CombiPatch™ therapy whereas they were noted to increase in Vivelle users. Shifts in mean TC/HDL-C were minimal after one year of therapy in both Vivelle and CombiPatch™ treatment groups. Decreases in triglycerides were observed in both CombiPatch™ and Vivelle in the *Continuous Combined* regimens and in the CombiPatch™-alone *Continuous Sequential* regimens.

The following tables summarize lipid parameters from these two clinical trials in 955 postmenopausal women (with intact uteri) after 1 year of therapy. Subjects were treated with (i) a continuous regimen of CombiPatch™ alone (*Continuous Combined* regimen), (ii) a sequential CombiPatch™ regimen consisting of an estradiol-only (VIVELLE® 0.05 mg) transdermal system followed by a CombiPatch™ transdermal system (*Continuous Sequential* regimen), or (iii) a continuous regimen with an estradiol-only transdermal system (VIVELLE® 0.05 mg). The values below represent mean percent change from baseline in patients with data at baseline and 1 year.

Lipid Profile Values, Adjusted Mean Percent Change from Baseline after One Year of *Continuous Combined* CombiPatch™ Transdermal Therapy

	CombiPatch™ Continuous Combined		VIVELLE® Continuous
Lipid Parameter (%)	0.05 / 0.14 mg per day[1] n = 122	0.05 / 0.25 mg per day[1] n = 99	0.05 mg per day n = 79
Total Cholesterol	-5.4%[2]	-8.6%[3]	-2.0%
HDL-C	-3.1%[3]	-9.1%[3]	+7.3%
LDL-C	-4.6%[4]	-7.6%[5]	-3.4%
Triglycerides	-4.6%	-9.5%	-6.7%

[1] Represents milligrams of estradiol/NETA delivered daily by each system
[2] Comparison with estradiol-only patch was significant ($p < 0.05$).
[3] Comparison with estradiol-only patch was significant ($p < 0.001$).
[4] Total number of patients with available data is 121.
[5] Total number of patients with available data is 97.

Lipid Profile Values, Adjusted Mean Percent Change from Baseline after One Year of *Continuous Sequential* CombiPatch™ Transdermal Therapy

	CombiPatch™ Continuous Sequential		VIVELLE® Continuous
Lipid Parameter (%)	0.05 / 0.14 mg per day[1] n = 117	0.05 / 0.25 mg per day[1] n = 115	0.05 mg per day n= 105
Total Cholesterol	-4.1%[2]	-9.0%[3]	-1.0%
HDL-C	-4.7%[3]	-8.9%[3]	+0.9%
LDL-C	-1.2%[4]	-6.8%[2,5]	-2.0%[6]
Triglycerides	-8.2%[3]	-14.1%[3]	+13.2%

[1] Represents milligrams of estradiol/NETA delivered daily by each system
[2] Comparison with estradiol-only patch was significant ($p < 0.05$).
[3] Comparison with estradiol-only patch was significant ($p < 0.001$).
[4] Total number of patients with available data is 116.
[5] Total number of patients with available data is 114.
[6] Total number of patients with available data is 103.

INDICATIONS AND USAGE

In women with an intact uterus, CombiPatch™ estradiol/NETA transdermal system is indicated for the following:

- Treatment of moderate-to-severe vasomotor symptoms associated with menopause
- Treatment of vulvar and vaginal atrophy

- Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure

CONTRAINDICATIONS

Estrogens/progestins combined should not be used in women under any of the following conditions or circumstances:

- Known or suspected pregnancy, including use for or as a diagnostic test for pregnancy. Estrogen or progestin may cause fetal harm when administered to a pregnant woman
- Known or suspected cancer of the breast
- Known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Active thrombophlebitis, thromboembolic disorders, or stroke
- Known hypersensitivity to estrogen, progestin, or to any CombiPatch™ transdermal system components

WARNINGS

ALL WARNINGS BELOW PERTAIN TO THE USE OF THIS COMBINATION PRODUCT.

Induction of Malignant Neoplasms

Endometrial Cancer: The reported endometrial cancer risk among users of unopposed estrogen is about 2- to 12-fold or 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 one year. The greatest risk appears to be associated with prolonged use—with increased risks of 15- to 24-fold for five 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. Other studies demonstrated a reduced risk of endometrial cancer or the risk returning to pre-estrogen treatment levels when a progestin was administered in combination with estrogen replacement therapy.

Clinical trials demonstrated that when progestin was administered with estrogen, as in the CombiPatch™ system, versus estrogen therapy alone, there is a markedly reduced incidence of endometrial hyperplasia (≤1% versus ≥20%, respectively), a possible precursor of endometrial cancer.

Breast Cancer: Some studies have reported a moderately increased risk of breast cancer (relative risk 1.3 to 2.0) in women on estrogen replacement therapy taking high doses, or in those taking low doses for prolonged periods of time, especially in excess of 10 years. The majority of studies, however, have not shown an association between breast cancer and women who have ever used estrogen replacement therapy. There is no conclusive evidence that concurrent progestin use alters the risk of breast cancer in long-term users of estrogen. (See **PRECAUTIONS**.)

Congenital Lesions with Malignant Potential: Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received 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. Although some of these changes are benign, others are precursors of malignancy.

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 risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women or from unopposed estrogen to combination estrogen/progestin therapy. However, to avoid the theoretical cardiovascular risk associated with high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

Hypercalcemia: Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, CombiPatch™ should be discontinued and appropriate measures should be taken to reduce the serum calcium level.

Thromboembolic Disorders: The physician should be alerted to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, CombiPatch™ should be discontinued immediately.

Visual Abnormalities: If there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine CombiPatch™ should be discontinued. If examination reveals papilledema or retinal vascular lesions, CombiPatch™ should be discontinued.

PRECAUTIONS

General: Based on experience with estrogens and/or progestins:

Endometrial Cancer: Progestins taken with estrogen drugs significantly reduce, but do not eliminate the risk of endometrial cancer that is associated with the use of estrogen. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when appropriate, should be undertaken to rule out malignancy in all cases of undiagnosed, persistent, or recurring abnormal vaginal bleeding. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

Use in Women Who Have Undergone Hysterectomy: Existing data do not support the use of the combination of estrogen and progestin in postmenopausal women without a uterus. (See *Addition of a Progestin.*)

Addition of a Progestin: There are possible risks that may be associated with the co-administration of a progestin in estrogen-based hormone replacement therapy. These risks, which include adverse effects on carbohydrate metabolism and impairment of glucose tolerance, have not been observed in CombiPatch™ clinical trials.

The possible enhancement of mitotic activity in breast epithelial tissue has also been reported with oral progestin therapy. While the effects of added progestins on the risk of breast cancer are unknown, available epidemiological 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.)

Physical Examination: A complete medical and family history should be taken before initiation of any estrogen therapy and periodically thereafter. The physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, as well as a cervical Papanicolaou test. Generally, estrogen should not be prescribed for longer than 1 year without another physical examination being performed.

Cardiovascular Effects: A causal relationship between estrogen replacement therapy and the 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 many 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 users, the following should be considered when interpreting these reports:

- 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 instead may 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
- 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 the favorable effects of estrogens on HDL levels as observed with CombiPatch™, although the norethindrone acetate in CombiPatch™ maintains the favorable effects of estrogens on LDL levels (See CLINICAL STUDIES.)

Gallbladder Disease: There is a reported 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in postmenopausal women receiving oral estrogens. Similar increases in gallbladder disease have not been reported with transdermal estradiol. Transdermal estrogen therapy does not increase biliary cholesterol saturation index; therefore, the risk may be diminished.

Elevated Blood Pressure: Occasional, reversible, blood pressure increases during oral estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, however, blood pressure has remained the same or has decreased.

Theoretically, in estrogen and progestin therapy, blood pressure elevations could be the result of increased renin substrate or angiotensin II levels, although these increases have not been reported in transdermal therapy.

Studies with CombiPatch™ showed no clinically significant changes in blood pressure among patients taking CombiPatch™. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

Fluid Retention: Because estrogens and/or progestins may cause some degree of fluid retention, careful observation is required when conditions that might be influenced by this factor are present (*e.g.*, asthma, epilepsy, migraine, and cardiac or renal dysfunction).

Uterine Bleeding and Mastodynia: Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding or mastodynia. In cases of undiagnosed abnormal bleeding, transvaginal ultrasonography or endometrial tissue sampling is generally appropriate, but evaluation should be based on the individual patient. (See **WARNINGS.**)

Collection of Pathological Specimens: The pathologist should be advised of estrogen/progestin therapy when relevant specimens are submitted.

Based on experience with estrogens or progestins:

Hypercoagulability: Recent retrospective case-controlled studies have reported an increased risk of venous thromboembolism (VTE) among current users of estrogen replacement therapy versus nonusers. This risk appears dose-duration dependent and is less pronounced than that associated with oral contraceptives. Although these studies found that estrogen use was associated with an increase in the relative risk of VTE, the absolute risk was low because of the infrequency of this event.

Because of the occasional occurrence of thrombotic disorders (thrombophlebitis, pulmonary embolism, retinal thrombosis, cerebrovascular disorders) and because there is insufficient information on hypercoagulability in women who have had previous thromboembolic disease, the benefit-risk of prescribing hormone replacement therapy should be reviewed individually for women with a past history of deep vein thrombosis or a family history of idiopathic thrombosis. The physician should be alert to the earliest manifestations of these disorders.

Familial Hyperlipoproteinemia: Oral estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism. Data from experience with CombiPatch™ and other transdermal estradiols regarding lipoproteins consistently show a reduction in triglycerides in postmenopausal women. Nonetheless, patients with familial hyperlipoproteinemia should be monitored closely when on estrogen therapy.

Lipoprotein Metabolism: See **CLINICAL STUDIES.**

Information for Patients: See Patient Package Insert included with this product.

Impaired Liver Function: Estrogens may be poorly metabolized in patients with impaired liver function. Although transdermally administered estrogen therapy avoids first-pass hepatic metabolism, estrogens should still be administered with caution in such patients.

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: The following laboratory tests may be altered by the use of estrogens or estrogen-progestin combination drugs (such as CombiPatch™):

- Prothrombin time, activated partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulation 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 activity; increased plasminogen antigen and activity
- Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels (by radioimmunoassay). T3 resin uptake is decreased, reflecting elevated TBG. Free T4 and free T3 concentrations are unaltered
- Other binding proteins may be altered in serum, *i.e.*,: increased corticosteroid binding globulin (CBG), leading to increased circulating corticosteroids, decreased SHBG. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin)
- Decreased serum total cholesterol, HDL-C and HDL_2-C subfraction, LDL-C, and triglycerides concentrations
- Reduced response to metyrapone test
- Reduced serum folate concentration
- Increased sulfobromophthalein retention

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, cervix, vagina, and liver. Long-term continuous administration of natural and synthetic progestins increases the frequency of benign liver tumors in male mice, but not in male or female rats. (See **CONTRAINDICATIONS** and **WARNINGS**.)

Norethindrone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

Pregnancy Category X: Estrogens should not be used during pregnancy. 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 the 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. Although some of these changes are benign, others are precursors of malignancy. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with subsequent increased risk of breast cancer in the mother, 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.

Several reports also suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses; some of these drugs induce mild virilization of the external genitalia of the female fetus.

Nursing Mothers: Detectable amounts of estradiol and norethindrone have been identified in the milk of mothers receiving these products and has been reported to decrease the quantity and quality of the milk. 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.

ADVERSE REACTIONS

See **WARNINGS,** and **PRECAUTIONS** regarding potential adverse effects on the fetus, induction of malignant neoplasms, cardiovascular disease, hypercalcemia, visual abnormalities, and adverse effects similar to those of oral contraceptives, including thromboembolism.

Table III: All Treatment Emergent Study Events Regardless of Relationship Reported at a Frequency of ≥ 5% with CombiPatch™
VASOMOTOR SYMPTOM STUDIES

	CombiPatch™ 0.05/0.14 mg per day[1] n = 113	CombiPatch™ 0.05/0.25 mg per day[1] n = 112	Placebo n = 107
Body as a Whole	46%	48%	41%
Abdominal pain	7%	6%	4%
Accidental injury	4%	5%	8%
Asthenia	8%	12%	4%
Back pain	11%	9%	5%
Flu syndrome	9%	5%	7%
Headache	18%	20%	20%
Pain	6%	4%	9%
Digestive	19%	23%	24%
Diarrhea	4%	5%	7%
Dyspepsia	1%	5%	5%
Flatulence	4%	5%	4%
Nausea	11%	8%	7%
Nervous	16%	28%	28%
Depression	3%	5%	9%
Insomnia	3%	6%	7%
Nervousness	3%	5%	1%
Respiratory	24%	38%	26%
Pharyngitis	4%	10%	2%

Respiratory disorder	7%	12%	7%
Rhinitis	7%	13%	9%
Sinusitis	4%	9%	9%
Skin and Appendages	8%	17%	16%
Application site reaction	2%	6%	4%
Urogenital	54%	63%	28%
Breast pain	25%	31%	7%
Dysmenorrhea	20%	21%	5%
Leukorrhea	5%	5%	3%
Menstrual Disorder	6%	12%	2%
Papanicolaou Smear Suspicious	8%	4%	5%
Vaginitis	6%	13%	5%

[1] Represents milligrams of estradiol/NETA delivered daily by each system

Table IV: All Treatment Emergent Study Events Regardless of Relationship Reported at a Frequency of ≥ 5% with CombiPatch™
ENDOMETRIAL HYPERPLASIA STUDIES

	CombiPatch™ 0.05/0.14 mg per day[1] n = 325	CombiPatch™ 0.05/0.25 mg per day[1] n = 312	Vivelle® 0.05 mg per day n =318
Body as a Whole	61%	60%	59%
Abdominal pain	12%	14%	16%
Accidental injury	10%	11%	8%
Asthenia	10%	13%	11%
Back pain	15%	14%	13%
Flu syndrome	14%	10%	7%
Headache	25%	17%	21%
Infection	5%	3%	3%
Pain	19%	15%	13%
Digestive	42%	32%	31%
Constipation	2%	5%	3%
Diarrhea	14%	9%	7%
Dyspepsia	8%	6%	5%
Flatulence	7%	5%	6%
Nausea	8%	12%	11%
Tooth Disorder	6%	4%	1%
Metabolic and Nutritional Disorders	12%	13%	11%
Peripheral edema	6%	6%	5%
Musculoskeletal	17%	17%	15%

Arthralgia	6%	6%	5%
Nervous	33%	30%	28%
Depression	8%	9%	8%
Dizziness	6%	7%	5%
Insomnia	8%	6%	4%
Nervousness	5%	6%	3%
Respiratory	45%	43%	40%
Bronchitis	5%	3%	4%
Pharyngitis	9%	9%	8%
Respiratory disorder	13%	9%	13%
Rhinitis	19%	22%	17%
Sinusitis	10%	12%	12%
Skin and Appendages	38%	37%	31%
Acne	4%	5%	4%
Application site reaction	20%	23%	17%
Rash	6%	5%	3%
Urogenital	71%	79%	74%
Breast Enlargement	2%	7%	2%
Breast pain	34%	48%	40%
Dysmenorrhea	30%	31%	19%
Leukorrhea	10%	8%	9%
Menorrhagia	2%	5%	9%
Menstrual Disorder	17%	19%	14%
Vaginal hemorrhage	3%	6%	12%
Vaginitis	9%	13%	13%

[1] Represents milligrams of estradiol/NETA delivered daily by each system

OVERDOSAGE

Overdosage with this dosage form is unlikely. Overdosage may cause nausea, and withdrawal bleeding may occur in females. Serious ill effects have not been reported following acute ingestion of large doses of estrogen/progestin-containing oral contraceptives by young children. In the event of a possible overdosage, the system should be removed immediately and medical attention sought.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: Treatment of postmenopausal symptoms is usually initiated during the menopausal stage when vasomotor symptoms occur.

Women not currently using continuous estrogen or combination estrogen/progestin therapy may start therapy with CombiPatch™ at any time. However, women currently using continuous estrogen or combination estrogen/progestin therapy should complete the current cycle of therapy, before initiating CombiPatch™ therapy. Women often experience withdrawal bleeding at the completion of the cycle. The first day of this bleeding would be an appropriate time to begin CombiPatch™ therapy.

Therapeutic Regimens: Combination estrogen/progestins regimens are indicated for women with an intact uterus. Two CombiPatch™ (17β-estradiol/NETA) transdermal delivery systems are available: 0.05 mg estradiol with 0.14 mg NETA per day (9 sq cm) and 0.05 mg estradiol with 0.25 mg NETA per day (16 sq cm). For all regimens, women should be reevaluated at 3- to 6-month intervals to determine if changes in hormone replacement therapy or if continued hormone replacement therapy is appropriate.

Continuous Combined Regimen: A CombiPatch™ 0.05 mg estradiol/0.14 mg NETA per day (9 sq cm) matrix transdermal system is worn continuously on the lower abdomen. Additionally, a dose of 0.05 mg estradiol/0.25 mg NETA (16 sq cm system) is available if a greater progestin dose is desired. A new system should be applied twice weekly during a 28-day cycle. Irregular bleeding may occur particularly in the first 6 months, but generally decreases with time, and often to an amennorheic state.

Continuous Sequential Regimen: CombiPatch™ can be applied as a sequential regimen in combination with an estradiol-only transdermal delivery system.

In this treatment regimen, an 0.05 mg per day (nominal delivery rate) estradiol transdermal system (VIVELLE®) is worn for the first 14 days of a 28-day cycle, replacing the system twice weekly according to product directions. For the remaining 14 days of the 28-day cycle, CombiPatch™ 0.05 mg estradiol/0.14 mg NETA per day (9 sq cm) transdermal system should be applied to the lower abdomen. Additionally, a dose of 0.05 mg estradiol / 0.25 mg NETA (16 sq cm system) is available if a greater progestin dose is desired. The CombiPatch™ system should be replaced twice weekly during this period in the cycle. Women should be advised that monthly withdrawal bleeding often occurs.

Application of the System: *Site Selection*: CombiPatch™ should be placed on a smooth (fold free), clean, dry area of the skin on the lower abdomen. **CombiPatch™ should not be applied to or near the breasts.** The area selected should not be oily (which can impair adherence of the system), damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off or modify drug delivery. The sites of application must be rotated, with an interval of at least one week allowed between applications to the same site.

Application: After opening the pouch, remove one side of the protective liner, taking care not to touch the adhesive part of the transdermal delivery system with the fingers. Immediately apply the transdermal delivery system to a smooth (fold free) area of skin on the lower abdomen. Remove the second side of the protective liner and press the system firmly in place with the hand for at least 10 seconds, making sure there is good contact, especially around the edges.

Care should be taken that the system does not become dislodged during bathing and other activities. If a system should fall off, the same system may be reapplied to another area of the lower abdomen. If necessary, a new transdermal system may be applied, in which case, the original treatment schedule should be continued. **Only one system should be worn at any one time during the 3- to 4-day dosing interval.**

Once in place, the transdermal system should not be exposed to the sun for prolonged periods of time.

Removal of the System: Removal of the system should be done carefully and slowly to avoid irritation of the skin. Should any adhesive remain on the skin after removal of the

system, allow the area to dry for 15 minutes. Then gently rubbing the area with an oil-based cream or lotion should remove the adhesive residue.

HOW SUPPLIED

CombiPatch™ estradiol/norethindrone acetate transdermal delivery system is available in:

System Size	Nominal Delivery Rate* Estradiol / Norethindrone Acetate	Presentation	NDC 0075-	Markings
9 sq cm	0.05 / 0.14 mg per day	8 systems per carton	0514-08	RPR 0514 or CombiPatch™ 0.05/0.14 mg per day
16 sq cm	0.05 / 0.25 mg per day	8 systems per carton	0525-08	RPR 0525 or CombiPatch™ 0.05/0.25 mg per day

*Nominal delivery rate described. See **DESCRIPTION** for more details regarding drug delivery.

Storage Conditions: Prior to dispensing to the patient, store refrigerated 2 to 8°C (36 to 46°F). After dispensing to the patient, CombiPatch™ can be stored at room temperature below 25°C (77°F) for up to 3 months. *For the Pharmacist:* When CombiPatch™ is dispensed to the patient, place an expiration date on the label. The date should not exceed either 3 months from the date of sale or the expiration date, whichever comes first.

Store the systems in the **sealed** foil pouch.

Do not store the system in areas where extreme temperatures can occur.

Keep out of the reach of children.

Rx only

Made in USA

VIVELLE® is a registered trademark of Novartis Pharmaceutical Corporation.

Manufactured for
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COLLEGEVILLE, PA 19426
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MIAMI FL 33186

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