

## CombiPatch<sup>®</sup>

(estradiol/norethindrone acetate transdermal system)

Rx only

### Prescribing Information

#### WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease or dementia. (See WARNINGS, Cardiovascular Disorders and Dementia.)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during five years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (see CLINICAL PHARMACOLOGY, Clinical Studies and WARNINGS, Cardiovascular Disorders and Malignant Neoplasms, *Breast Cancer*).

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during four years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL PHARMACOLOGY, Clinical Studies, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use.)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

#### DESCRIPTION

CombiPatch<sup>®</sup> (estradiol/norethindrone acetate transdermal system) is an adhesive-based matrix transdermal patch designed to release both 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 <sup>1</sup> (mg)	Nominal Delivery Rate <sup>2</sup> (mg per day) Estradiol/NETA
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9 sq cm round	0.62	2.7	0.05/0.14
16 sq cm round	0.51	4.8	0.05/0.25

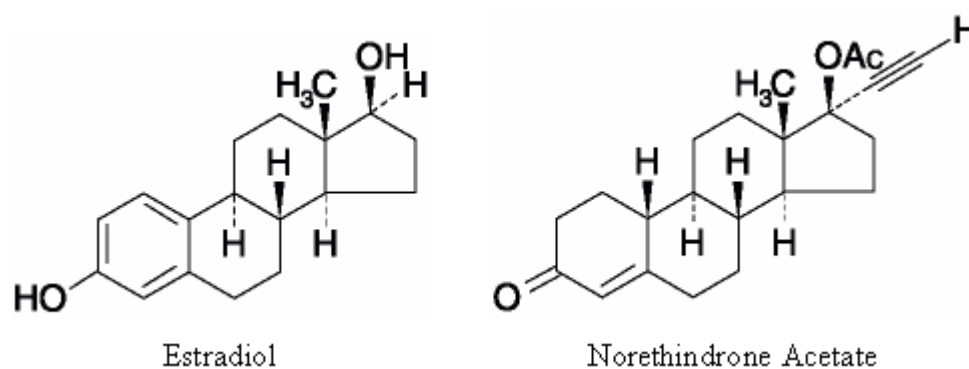
<sup>1</sup> NETA = norethindrone acetate.

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

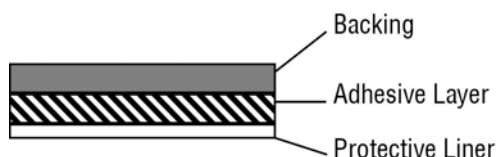
Estradiol USP (estradiol) is a white to creamy white, odorless, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17 $\beta$ -diol. The molecular weight of estradiol is 272.39 and the molecular formula is C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>.

Norethindrone acetate USP is a white to creamy white, odorless, crystalline powder, chemically described as 17-hydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one acetate. The molecular weight of norethindrone acetate is 340.47 and the molecular formula is C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>.

The structural formulas for estradiol and norethindrone acetate are



CombiPatch transdermal systems are comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film backing, (2) an adhesive layer containing estradiol, norethindrone acetate, acrylic adhesive, silicone adhesive, oleyl alcohol, oleic acid NF, povidone USP and dipropylene glycol, and (3) a polyester release protective liner, which is attached to the adhesive surface and must be removed before the system can be used.



The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive.

## CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level. The primary source of estrogen in normally cycling

adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone 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. These vary in proportion from tissue to tissue.

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

## Pharmacokinetics

### Absorption

**Estradiol:** Estrogens used in hormone therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. Administration of CombiPatch every three to four 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)**

<i>Estradiol</i>				
System Size	Dose Estradiol/NETA (mg per day)	C <sub>max</sub>	C <sub>min</sub>	C <sub>avg</sub>
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)
<i>Estrone</i>				
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 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**

<b>System Size</b>	<b>Dose Estradiol/NETA (mg per day)</b>	<b>C<sub>max</sub></b>	<b>C<sub>min</sub></b>	<b>C<sub>avg</sub></b>
9 sq cm	0.05/0.14	617 (341)	386 (137)	489 (244)
16 sq cm	0.05/0.25	1,060 (543)	686 (306)	840 (414)

### ***Distribution***

***Estradiol:*** 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.

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

### ***Metabolism***

***Estradiol:*** 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. 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.

***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.

## **Excretion**

**Estradiol:** Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Estradiol has a short elimination half-life of approximately two to three hours; therefore, a rapid decline in serum levels is observed after the CombiPatch estradiol/norethindrone acetate transdermal system is removed. Within four to eight 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 one year).

**Norethindrone:** The elimination half-life of norethindrone is reported to be six to eight 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 one year).

## **Special Populations**

CombiPatch has been studied only in postmenopausal women.

## **Drug Interactions**

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

## **Adhesion**

Averaging across six clinical trials lasting three months to one year, of 1,287 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.

## **Clinical Studies**

### **Effects on Vasomotor Symptoms**

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<sup>®</sup> 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

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

<sup>1</sup> Means were adjusted for imbalance among treatment groups and investigators (least squares mean from ANOVA).

<sup>2</sup> Represents the milligrams of estradiol/norethindrone acetate delivered daily by each system.

<sup>3</sup> Population represents those patients who had baseline and endpoint observations.

<sup>4</sup> 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).

<sup>5</sup> P value versus placebo = <0.001.

<sup>6</sup> Total number of patients with available data is 56.

<sup>7</sup> 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 <sup>1</sup>	CombiPatch® Continuous Sequential		Placebo
	0.05/0.14 mg per day <sup>2</sup> n=54	0.05/0.25 mg per day <sup>2</sup> n=59	n=53
	Number of Hot Flushes <sup>3</sup>	-9.3 <sup>5</sup>	-9.5 <sup>5</sup>
Daily Intensity of Hot Flushes <sup>3,4</sup>	-4.4 <sup>5</sup>	-4.5 <sup>5</sup>	-2.1

<sup>1</sup> Means were adjusted for imbalance among treatment groups and investigators (least squares mean from ANOVA).

<sup>2</sup> Represents the milligrams of estradiol/norethindrone acetate delivered daily by each system.

<sup>3</sup> Population represents those patients who had baseline and endpoint observations.

<sup>4</sup> 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).

<sup>5</sup> P value versus placebo = <0.001.

### **Effects on the Endometrium**

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 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 regimen has not been shown to interfere with the efficacy of estrogen therapy for its approved indications.

CombiPatch was effective in reducing the incidence of estrogen-induced endometrial hyperplasia after one 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 one 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**

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

<sup>1</sup> Represents milligrams of estradiol/NETA delivered daily by each system.

<sup>2</sup> Biopsy after 12 cycles of treatment or hyperplasia before cycle 12.

<sup>3</sup> Comparison of continuous combined regimen versus estradiol-only patch was significant (p value <0.001).

<sup>4</sup> This patient had hyperplasia at baseline.

<sup>5</sup> One of 39 patients had hyperplasia in an endometrial polyp.

## Incidence of Endometrial Hyperplasia in a *Continuous Sequential CombiPatch*<sup>®</sup> Regimen

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

<sup>1</sup> Represents milligrams of estradiol/NETA delivered daily by each system.

<sup>2</sup> Biopsy after 12 cycles of treatment or hyperplasia before cycle 12.

<sup>3</sup> Comparison of continuous sequential regimen versus estradiol-only patch was significant (p value <0.001).

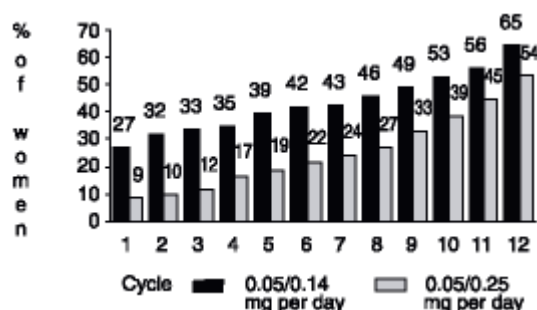
<sup>4</sup> This patient had hyperplasia at baseline.

<sup>5</sup> This patient had hyperplasia in an endometrial polyp.

### Effects on Uterine Bleeding or Spotting

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 four and six 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<sup>®</sup> *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

In the CE/MPA substudy of the WHI (n=16,608 predominantly healthy postmenopausal women) hormone therapy lowered the level of low-density lipoprotein (LDL) cholesterol and

increased the level of high-density lipoprotein (HDL), yet an increased risk of coronary heart disease events was observed. Therefore, estrogens and progestins should not be used for the prevention of cardiovascular disease. (See BOXED WARNING and CLINICAL PHARMACOLOGY, Clinical Studies.)

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 regimens.

The following tables summarize lipid parameters from these two clinical trials in 955 postmenopausal women (with intact uteri) after one 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 one year.

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

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

<sup>1</sup> Represents milligrams of estradiol/NETA delivered daily by each system.

<sup>2</sup> Comparison with estradiol-only patch was significant (p <0.05).

<sup>3</sup> Comparison with estradiol-only patch was significant (p <0.001).

<sup>4</sup> Total number of patients with available data is 121.

<sup>5</sup> 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*<sup>®</sup> Transdermal Therapy

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

<sup>1</sup> Represents milligrams of estradiol/NETA delivered daily by each system.

<sup>2</sup> Comparison with estradiol-only patch was significant (p <0.05).

<sup>3</sup> Comparison with estradiol-only patch was significant (p <0.001).

<sup>4</sup> Total number of patients with available data is 116.

<sup>5</sup> Total number of patients with available data is 114.

<sup>6</sup> Total number of patients with available data is 103.

### Women's Health Initiative Studies

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

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79, 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table III below.

**Table III. Relative and Absolute Risk Seen in the CE/MPA Substudy of WHI<sup>a</sup>**

Event <sup>c</sup>	Relative Risk CE/MPA vs. Placebo at 5.2 Years (95% CI*)	Placebo n=8,102	CE/MPA n=8,506
Absolute Risk per 10,000 Women-Years			
CHD Events	1.29 (1.02-1.63)	30	37
Nonfatal MI	1.32 (1.02-1.72)	23	30
CHD Death	1.18 (0.70-1.97)	6	7
Invasive Breast Cancer <sup>b</sup>	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary Embolism	2.13 (1.39-3.25)	8	16
Colorectal Cancer	0.63 (0.43-0.92)	16	10
Endometrial Cancer	0.83 (0.47-1.47)	6	5
Hip Fracture	0.66 (0.45-0.98)	15	10
Death Due to Causes Other than the Events Above	0.92 (0.74-1.14)	40	37
Global Index <sup>c</sup>	1.15 (1.03-1.28)	151	170
Deep Vein Thrombosis <sup>d</sup>	2.07 (1.49-2.87)	13	26
Vertebral Fractures <sup>d</sup>	0.66 (0.44-0.98)	15	9
Other Osteoporotic Fractures <sup>d</sup>	0.77 (0.69-0.86)	170	131

<sup>a</sup>Adapted from JAMA, 2002; 288: 321-333.

<sup>b</sup>Includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer.

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

<sup>d</sup>Not included in global index.

\* Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

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

### Women’s Health Initiative Memory Study

The Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were aged 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of oral CE/MPA (0.625 mg conjugated equine estrogens plus 2.5 mg

medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of four years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See BOXED WARNING and WARNINGS, Dementia.)

## INDICATIONS AND USAGE

In women with an intact uterus, CombiPatch is indicated for the following:

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

When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

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

## CONTRAINDICATIONS

CombiPatch should not be used in women under any of the following conditions:

- Undiagnosed abnormal genital bleeding.
- Known, suspected, or history of cancer of the breast.
- Known or suspected estrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism or history of these conditions.
- Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
- Liver dysfunction or disease.
- CombiPatch should not be used in patients with known hypersensitivity to its ingredients.
- Known or suspected pregnancy. There is no indication for CombiPatch in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (see PRECAUTIONS).

## **WARNINGS**

See BOXED WARNING.

### **Cardiovascular Disorders**

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens/progestins should be discontinued immediately.

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

### **Coronary Heart Disease and Stroke**

In the Women's Health Initiative (WHI) study, an increase in the number of strokes was observed in women receiving CE alone compared to placebo.

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

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

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

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

## **Venous Thromboembolism (VTE)**

In the Women's Health Initiative (WHI) study, an increase in VTE was observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See CLINICAL PHARMACOLOGY, Clinical Studies.)

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

## **Malignant Neoplasms**

### ***Breast Cancer***

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see CLINICAL PHARMACOLOGY, Clinical Studies). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen-alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen-alone and/or estrogen/progestin-combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 versus 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the

two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

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

### **Endometrial Cancer**

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among 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 associated with prolonged use with increased risks of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

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

### **Dementia**

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of four years, 40 women being treated with CE/MPA (1.8%, n=2,229) and 21 women in the placebo group (0.9%, n=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21–3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL PHARMACOLOGY, Clinical Studies and PRECAUTIONS, Geriatric Use.)

### **Gallbladder Disease**

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

## **Hypercalcemia**

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

## **Visual Abnormalities**

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

## **PRECAUTIONS**

### **General**

#### ***Addition of a Progestin When a Woman Has Not Had a Hysterectomy***

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

#### ***Elevated Blood Pressure***

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

#### ***Hypertriglyceridemia***

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

#### ***Impaired Liver Function and Past History of Cholestatic Jaundice***

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

#### ***Hypothyroidism***

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T<sub>4</sub> and T<sub>3</sub> 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.

### ***Fluid Retention***

Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

### ***Hypocalcemia***

Estrogens should be used with caution in individuals with severe hypocalcemia.

### ***Ovarian Cancer***

The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77–3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

### ***Exacerbation of Endometriosis***

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

### ***Exacerbation of Other Conditions***

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

### **Patient Information**

Physicians are advised to discuss the **Patient Information** leaflet with patients for whom they prescribe CombiPatch.

### **Laboratory Tests**

Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradiol, FSH).

### **Drug/Laboratory Test Interactions**

- 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.

- Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T<sub>4</sub> levels (by column or by radioimmunoassay) or T<sub>3</sub> levels by radioimmunoassay. T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG. Free T<sub>4</sub> and free T<sub>3</sub> concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
- 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 hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
- Impaired glucose tolerance.
- Reduced response to metyrapone test.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See BOXED WARNING, WARNINGS and PRECAUTIONS.)

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.

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

### **Pregnancy**

CombiPatch should not be used during pregnancy. (See CONTRAINDICATIONS.)

### **Nursing Mothers**

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens and progestins have been identified in the milk of mothers receiving these drugs. Caution should be exercised when CombiPatch is administered to a nursing mother.

### **Pediatric Use**

CombiPatch is not indicated for use in children.

### **Geriatric Use**

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of four years, 82% (n=3,729) were 65 to 74 while 18% (n=803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most

common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See WARNINGS, Dementia.)

## ADVERSE REACTIONS

See BOXED WARNING, WARNINGS and PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

**Table IV. All Treatment Emergent Study Events Regardless of Relationship Reported at a Frequency of  $\geq 5\%$  with CombiPatch<sup>®</sup>**

	<b>VASOMOTOR SYMPTOM STUDIES</b>		
	<b>CombiPatch<sup>®</sup></b> 0.05/0.14 mg per day <sup>1</sup> n=113	<b>CombiPatch<sup>®</sup></b> 0.05/0.25 mg per day <sup>1</sup> n=112	<b>Placebo</b> n=107
<i>Body as a Whole</i>	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%
<i>Digestive</i>	19%	23%	24%
Diarrhea	4%	5%	7%
Dyspepsia	1%	5%	5%
Flatulence	4%	5%	4%
Nausea	11%	8%	7%
<i>Nervous</i>	16%	28%	28%
Depression	3%	5%	9%
Insomnia	3%	6%	7%
Nervousness	3%	5%	1%
<i>Respiratory</i>	24%	38%	26%
Pharyngitis	4%	10%	2%
Respiratory Disorder	7%	12%	7%
Rhinitis	7%	13%	9%
Sinusitis	4%	9%	9%
<i>Skin and Appendages</i>	8%	17%	16%
Application Site Reaction	2%	6%	4%
<i>Urogenital</i>	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%

<sup>1</sup>Represents milligrams of estradiol/NETA delivered daily by each system.

**Table V. All Treatment Emergent Study Events Regardless of Relationship Reported at a Frequency of  $\geq 5\%$  with CombiPatch<sup>®</sup>**

<b>ENDOMETRIAL HYPERPLASIA STUDIES</b>			
	<b>CombiPatch<sup>®</sup></b>	<b>CombiPatch<sup>®</sup></b>	<b>Vivelle<sup>®</sup></b>
	0.05/0.14 mg per day <sup>1</sup> n=325	0.05/0.25 mg per day <sup>1</sup> n=312	0.05 mg per day n=318
<i>Body as a Whole</i>	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%
<i>Digestive</i>	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%
<i>Metabolic and Nutritional Disorders</i>	12%	13%	11%
Peripheral Edema	6%	6%	5%
<i>Musculoskeletal</i>	17%	17%	15%
Arthralgia	6%	6%	5%
<i>Nervous</i>	33%	30%	28%
Depression	8%	9%	8%
Dizziness	6%	7%	5%
Insomnia	8%	6%	4%
Nervousness	5%	6%	3%
<i>Respiratory</i>	45%	43%	40%
Bronchitis	5%	3%	4%
Pharyngitis	9%	9%	8%
Respiratory Disorder	13%	9%	13%
Rhinitis	19%	22%	17%
Sinusitis	10%	12%	12%
<i>Skin and Appendages</i>	38%	37%	31%
Acne	4%	5%	4%
Application Site Reaction	20%	23%	17%
Rash	6%	5%	3%
<i>Urogenital</i>	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%

<sup>1</sup>Represents milligrams of estradiol/NETA delivered daily by each system.

The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

### **Genitourinary System**

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea, increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

### **Breasts**

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

### **Cardiovascular**

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

### **Gastrointestinal**

Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.

### **Skin**

Chloasma or melasma, that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

### **Eyes**

Retinal vascular thrombosis, intolerance to contact lenses.

### **Central Nervous System**

Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

### **Miscellaneous**

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

## **OVERDOSAGE**

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

When estrogen therapy is prescribed for a postmenopausal woman with a uterus, a progestin should be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine whether treatment is still necessary (see BOXED WARNING and WARNINGS). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

### Initiation of Therapy

Treatment of postmenopausal symptoms is usually initiated during the menopausal stage when vasomotor symptoms occur. Patients should be started at the lowest dose. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. The lowest effective dose of CombiPatch has not been determined in clinical trials.

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/progestin regimens are indicated for women with an intact uterus. Two CombiPatch (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). The lowest effective dose should be used. For all regimens, women should be reevaluated at 3- to 6-month intervals to determine if changes in hormone therapy or if continued hormone 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 six months, but generally decreases with time, and often to an amenorrheic 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 rub the area with an oil-based cream or lotion to remove the adhesive residue.

## HOW SUPPLIED

CombiPatch<sup>®</sup> estradiol/norethindrone acetate transdermal delivery system is available in:

<u>System Size</u>	<u>Nominal Delivery Rate*</u> <u>Estradiol/Norethindrone Acetate</u>	<u>Presentation</u>	<u>NDC</u>	<u>Markings</u>
9 sq cm	0.05/0.14 mg per day	8 systems per carton	0078-0377-42	CombiPatch 0.05/0.14 mg per day
		Cartons of 3 patient packs	0078-0377-45	

		of 8 systems		
16 sq cm	0.05/0.25 mg per day	8 systems per carton	0078-0378-42	CombiPatch 0.05/0.25 mg per day
		Cartons of 3 patient packs of 8 systems	0078-0378-45	

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

### Storage Conditions

Prior to dispensing to the patient, store refrigerated 2-8°C (36-46°F). After dispensing to the patient, CombiPatch can be stored at room temperature below 25°C (77°F) for up to six months. **For the Pharmacist:** When CombiPatch is dispensed to the patient, place an expiration date on the label. The date should not exceed either six 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 this and all medicines out of the reach of children.**

Vivelle<sup>®</sup> is a registered trademark of Novartis Pharmaceuticals Corporation.

## PATIENT INFORMATION

### CombiPatch®

*(estradiol/norethindrone acetate transdermal system)*

#### **Rx only**

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

#### **WHAT IS THE MOST IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT COMBIPATCH (A COMBINATION OF ESTROGEN AND PROGESTIN HORMONES)?**

- Do not use estrogens and progestins to prevent heart disease, heart attacks, strokes, or dementia.

Using estrogens and progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens and progestins may increase your risk of dementia. You and your health care provider should talk regularly about whether you still need treatment with CombiPatch.

#### ***What is CombiPatch?***

CombiPatch is a medicine that contains two kinds of hormones, estrogen and progestin.

CombiPatch is available in two round sizes:

<b>System Size</b>	<b>Amount of Each Drug in Each System Estradiol/NETA (mg)</b>	<b>Amount of Each Drug Released Every Day Estradiol/NETA (mg per day)</b>
9 sq cm	0.62/2.7	0.05/0.14
16 sq cm	0.51/4.8	0.05/0.25

#### ***What is CombiPatch used for?***

CombiPatch is used after menopause to:

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

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

- **Treat moderate to severe dryness, itching and burning in or around the vagina.** You and your health care provider should talk regularly about whether you still need treatment with CombiPatch to control these problems. If you use CombiPatch only to treat your dryness, itching, and burning in and around your vagina, talk with your health care provider about whether a topical vaginal product would be better for you.
- **Treat certain conditions in which a young woman’s ovaries do not produce enough estrogens naturally.**

### ***Who should not use CombiPatch?***

**Do not use CombiPatch if you have had your uterus removed (hysterectomy).**

CombiPatch contains a progestin to decrease the chances of getting cancer of the uterus. If you do not have a uterus, you do not need a progestin and you should not take CombiPatch.

Do not start using CombiPatch if you:

- **Have unusual vaginal bleeding.**
- **Currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your health care provider about whether you should take CombiPatch.
- **Had a stroke or heart attack in the recent past (for example in the past year).**
- **Currently have or have had blood clots.**
- **Currently have or have had liver problems.**
- **Are allergic to CombiPatch or any of its ingredients.** See the end of this leaflet for a list of ingredients in CombiPatch.
- **Think you may be, or know that you are, pregnant.**

### ***Tell your health care provider:***

**If you are breast-feeding.** The hormones in CombiPatch can pass into your milk.

- **About all of your medical problems.** Your health care provider may need to check you more carefully if you have certain conditions such as asthma (wheezing), epilepsy

(seizures), migraine, endometriosis, lupus, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

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

### ***How should you use CombiPatch?***

- Start at the lowest dose and talk to your health care provider about how well that dose is working for you.
- Estrogens and progestins should be used at the lowest dose possible for your treatment, only as long as needed. The lowest effective dose of CombiPatch has not been determined in clinical trials. You and your health care provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with CombiPatch.

CombiPatch is a thin, opaque, plastic patch that sticks to the skin. Each patch is sealed in a pouch that protects it until you are ready to put it on. Do not open the pouch or remove a patch until just before you apply it.

### ***How often should you apply CombiPatch?***

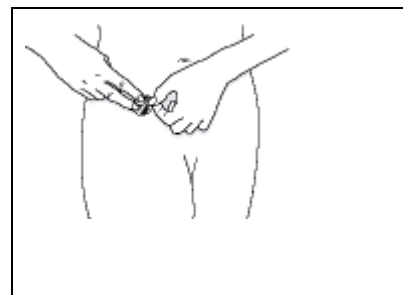
- Put on a new CombiPatch every 3 to 4 days, according to your health care provider's instructions.
- Wear the patch all the time until it is time to replace it with a new patch.
- **Change the patch on the same days each week.** Your CombiPatch package contains a calendar checklist to help you remember a schedule. Mark the 2-day schedule you plan to follow.
- **Only one CombiPatch should be worn at any one time.**

### ***Where do you apply CombiPatch?***

CombiPatch should be placed on the lower abdomen (below the panty line).

For best results, choose:

- A smooth (fold-free), clean, dry area of skin.
- An area that has been freshly washed and dried well (free of oils, lotions or powders that could keep the patch from



sticking well to your skin).

- An area that has no cuts, rashes, or other skin problems.

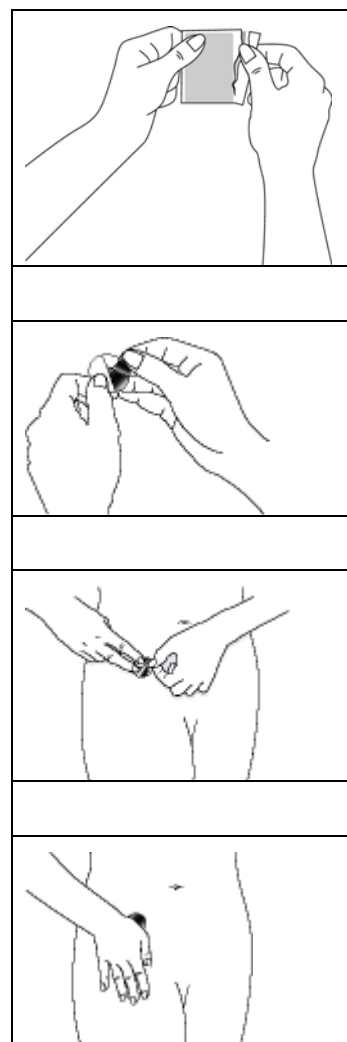


Every time you put on a new CombiPatch, move to a different area on your lower abdomen than used before. The same area should not be used again for at least 1 week.

**Do not put CombiPatch on or near your breasts.** You should not put CombiPatch on the waistline, since tight clothing may rub off the patch. To avoid disturbing the patch it may help to choose an area where your underwear will cover it all the time.

### ***How do you apply CombiPatch?***

- Each CombiPatch is sealed in its own protective pouch. Tear open this pouch at the slit (do not use scissors) and remove the patch. The pouch should not be opened until you are ready to put the patch on.
- A protective liner covers the adhesive side of the patch. Peel off one side of the protective liner. Do not touch the sticky part of the patch with your fingers.
- Put the sticky side of the patch on an area of skin on your lower abdomen. Peel off the second side of the protective liner.
- Press the patch firmly in place with your hand for about 10 seconds. Make sure there is good contact, especially around the edges.



When changing CombiPatch, peel off the used patch slowly. Fold the used patch in half (sticky sides together) and throw it in the trash. **Please remember to keep CombiPatch out of the reach of children.**

If any adhesive remains on your skin after removal of the patch, let the area dry for 15 minutes. Then gently rub the area with an oil-based cream or lotion to remove the adhesive from your skin.

### ***What if you forget to put on a new CombiPatch?***

If you are currently wearing a patch, remove it and put on a new patch in a different area of your lower abdomen. Then go back to changing the patch on the same days each week.

***Can you wear CombiPatch when bathing, swimming, or in the sun?***

- Bathing, swimming, or showering should not affect the patch. Make sure that the patch does not loosen during these activities.
- The patch should not be exposed to the sun for long periods of time. Once in place, make sure that the patch is covered by your clothing (but remember not to apply CombiPatch on or near your breasts).

***What should you do if CombiPatch comes off?***

Most women find that CombiPatch seldom comes off. But if a patch should fall off, the same patch may be put on a different area of the lower abdomen (make sure you are choosing a clean, dry, lotion-free area of skin). If the patch will not stick completely to your skin, put a new CombiPatch on a different area of the lower abdomen. No matter what day this happens, go back to changing the patch on the same days each week.

***What are the possible side effects of estrogens?***

**Less common but serious side effects include:**

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

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

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

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

**Common side effects include:**

- Headache

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

**Other side effects include:**

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

Other side effects of CombiPatch are possible. For more information, ask your health care provider or pharmacist.

***What can you do to lower your chances of a serious side effect with CombiPatch?***

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

***General information about the safe and effective use of CombiPatch***

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

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

***What are the ingredients in CombiPatch?***

CombiPatch transdermal systems are comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film backing, (2) an adhesive layer containing estradiol, norethindrone acetate, acrylic adhesive, silicone adhesive, oleyl alcohol, oleic acid NF, povidone USP and dipropylene glycol, and (3) a polyester release protective liner, which is attached to the adhesive surface and must be removed before the system can be used. The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive.

***Where should you store CombiPatch?***

Each CombiPatch is sealed in its own pouch. To protect the medication, store the patch in the pouch until you are ready to use it.

Before CombiPatch was sold to you, the pharmacist stored the package in the refrigerator. **You can store CombiPatch at room temperature, below 77°F (25°C).** The patch sticks best to your skin when stored at room temperature. For best results, **DO NOT** store CombiPatch patches in the refrigerator or in areas where the temperature can become extreme (very high or very low), such as in **DIRECT SUNLIGHT** or in a car.

**Keep this and all medicines out of the reach of children.**

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