CombiPatch®

(estradiol/norethindrone acetate transdermal system)

Rx only

Prescribing Information

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER, ENDOMETRIAL CANCER, AND PROBABLE DEMENTIA

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. (See CLINICAL STUDIES and WARNINGS, Cardiovascular Disorders and Probable Dementia).

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported an increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. (See CLINICAL STUDIES and WARNINGS, Cardiovascular Disorders).

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL STUDIES and WARNINGS, Probable Dementia and PRECAUTIONS, Geriatric Use).

Breast Cancer

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer. (See CLINICAL STUDIES and WARNINGS, Malignant Neoplasms, Breast Cancer).

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

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.

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or

recurring abnormal genital bleeding. (See WARNINGS, Malignant Neoplasms, Endometrial Cancer).

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. (See CLINICAL STUDIES and WARNINGS, Cardiovascular Disorders and Probable Dementia).

The WHI estrogen-alone substudy reported increased risks of stroke and DVT in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral CE (0.625 mg)-alone, relative to placebo. (See CLINICAL STUDIES and WARNINGS, Cardiovascular Disorders).

The WHIMS estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL STUDIES and WARNINGS, Probable Dementia and PRECAUTIONS, Geriatric Use).

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

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

Two systems are available, providing the following *in vivo* delivery rates of estradiol and NETA.

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

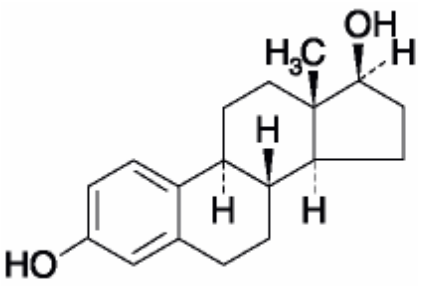
[1]NETA=norethindrone acetate.

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

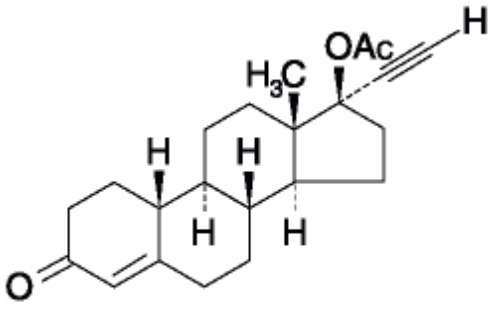
Estradiol USP (estradiol) is a white to creamy white, odorless, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. The molecular weight of estradiol is 272.39 and the molecular formula is $C_{18}H_{24}O_2$.

NETA 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 NETA is 340.47 and the molecular formula is $C_{22}H_{28}O_3$.

The structural formulas for estradiol and NETA are:

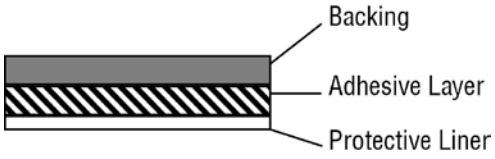


Estradiol



Norethindrone Acetate

CombiPatch is comprised of 3 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, NETA, acrylic adhesive, silicone adhesive, 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 NETA 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 in the 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, 2 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 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 1 study, serum concentrations of estradiol were measured in 40 healthy, postmenopausal women throughout 3 consecutive CombiPatch applications to the abdomen (each dose was applied for three 3.5-day periods). The corresponding pharmacokinetic parameters are summarized in Table 1.

Table 1. Mean (SD) Serum Estradiol and Estrone Concentrations (pg/mL) at Steady-State (Uncorrected for Baseline Levels)

		Estradiol		
System Size	**Dose Estradiol/NETA (mg per day)**	**C_{max}**	**C_{min}**	**C_{avg}**
9 cm^2	0.05/0.14	71 (32)	27 (17)	45 (21)
16 cm^2	0.05/0.25	71 (30)	37 (17)	50 (21)
		Estrone		
9 cm^2	0.05/0.14	72 (23)	49 (19)	54 (19)
16 cm^2	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 NETA.

In 1 study, serum concentrations of norethindrone were measured in 40 healthy, postmenopausal women throughout 3 consecutive CombiPatch applications to the abdomen (each dose was applied for three 3.5-day periods). The corresponding pharmacokinetic parameters are summarized in Table 2.

Table 2. 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 cm^2	0.05/0.14	617 (341)	386 (137)	489 (244)
16 cm^2	0.05/0.25	1060 (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 percent 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 a 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 intestine 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.

Norethindrone: NETA is hydrolyzed to the active moiety, norethindrone, in most tissues including skin and blood. Norethindrone is primarily metabolized in the liver.

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 2 to 3 hours; therefore, a rapid decline in serum levels is observed after the CombiPatch estradiol/NETA transdermal system is removed. Within 4 to 8 hours serum estradiol concentrations return to untreated, postmenopausal levels (less than 20 pg/mL).

Concentration data from clinical trials 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: 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 clinical trials 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).

Special Populations

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions

No drug interaction studies have been conducted with CombiPatch. *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 (*Hypericum perforatum*) preparations, anticonvulsants (e.g., phenobarbital, phenytoin and carbamazepine), phenylbutazone, and anti-infectives (e.g., rifampin, rifabutin, nevirapine and efavirenz) 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, nelfinavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Adhesion

Averaging across 6 clinical trials lasting 3 months to 1 year, of 1,287 patients treated, CombiPatch transdermal systems completely adhered to the skin nearly 90 percent of the time over the 3- to 4-day wear period. Less than 2 percent of the patients required reapplication or replacement of systems due to lifting or detachment. Two patients (0.2 percent) discontinued therapy during clinical trials due to adhesion failure.

CLINICAL STUDIES

Effects on Vasomotor Symptoms

In 2 clinical trials designed to assess the degree of relief of moderate to severe vasomotor symptoms in postmenopausal women (n=332), CombiPatch was administered for 3 28-day cycles in *Continuous Combined* or *Continuous Sequential* treatment regimens versus placebo. In the *Continuous Combined* regimen, CombiPatch was applied throughout the 3 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 3 and 4)

Table 3. 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/NETA 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.

Table 4. Adjusted Mean Change in the Number of Hot Flushes and Daily Intensity of Hot Flushes per Day in CombiPatch *Continuous Sequential* Transdermal Therapy

	CombiPatch Continuous Sequential		Placebo
Adjusted Mean Change from Baseline[1]	**0.05/0.14 mg per day[2] n=54**	**0.05/0.25 mg per day[2] n=59**	**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/NETA 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.

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 1 year of therapy in two 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. Tables 5 and 6 summarize these results (intent-to-treat populations).

Table 5. 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
Number of Patients with Biopsies[2]	123	98	103
Number (%) 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 ($p < 0.001$).

[4]This patient had hyperplasia at baseline.

[5]One of 39 patients had hyperplasia in an endometrial polyp.

Table 6. Incidence of Endometrial Hyperplasia in a *Continuous Sequential* CombiPatch Regimen

	CombiPatch Continuous Sequential 0.05/0.14 mg per day[1]	CombiPatch Continuous Sequential 0.05/0.25 mg per day[1]	Vivelle Continuous 0.05 mg per day
Number of Patients with Biopsies[2]	117	114	115
Number (%) 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 ($p < 0.001$).

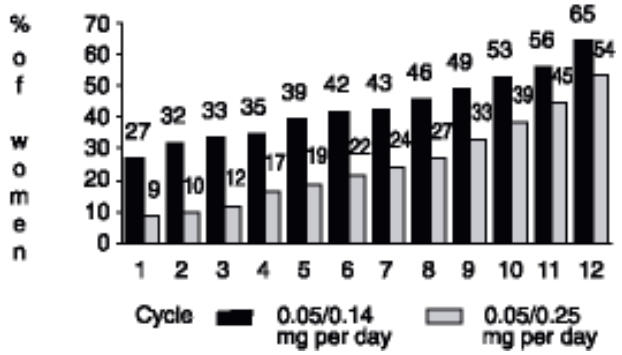
[4]This patient had hyperplasia at baseline.

[5]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 1-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 percent and 39 percent 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. (See Figure 1)

Figure 1. Incidence of Cumulative Amenorrhea* in CombiPatch *Continuous Combined* Transdermal Therapy by Cycle Over a 1-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.

Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) [defined as nonfatal MI, silent MI and CHD death], with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other cause. These substudies did not evaluate the effects of CE plus MPA or CE-alone on menopausal symptoms.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79 years; 83.9 percent white, 6.8 percent black, 5.4 percent Hispanic, 3.9 percent Other), are presented in Table 7. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 7. Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[c])	CE/MPA n=8,506	Placebo n=8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99–1.53)	41	34
Nonfatal MI	*1.28 (1.00–1.63)*	*31*	*25*
CHD death	*1.10 (0.70–1.75)*	*8*	*8*
All strokes	1.31 (1.03–1.68)	33	25
Ischemic stroke	*1.44 (1.09–1.90)*	*26*	*18*
Deep vein thrombosis[d]	1.95 (1.43–2.67)	26	13
Pulmonary embolism	2.13 (1.45–3.11)	18	8
Invasive breast cancer[e]	1.24 (1.01–1.54)	41	33
Colorectal cancer	0.61 (0.42–0.87)	10	16
Endometrial cancer[d]	0.81 (0.48–1.36)	6	7
Cervical cancer[d]	1.44 (0.47–4.42)	2	1
Hip fracture	0.67 (0.47–0.96)	11	16
Vertebral fractures[d]	0.65 (0.46–0.92)	11	17
Lower arm/wrist fractures[d]	0.71 (0.59–0.85)	44	62
Total fractures[d]	0.76 (0.69–0.83)	152	199
Overall mortality[f]	1.00 (0.83–1.19)	52	52
Global Index[g]	1.13 (1.02–1.25)	184	165

[a]Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b]Results are based on centrally adjudicated data.
[c]Nominal confidence intervals (CI) unadjusted for multiple looks and multiple comparisons.
[d]Not included in "global index".
[e]Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.
[f]All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
[g]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, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age a nonsignificant trend toward reduced risk for overall mortality [hazard ratio (HR) 0.69 (95 percent CI 0.44 to 1.07)].

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79 years; 75.3 percent white, 15.1 percent black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in Table 8.

Table 8. Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[b])	CE n=5,310	Placebo n=5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78–1.16)	54	57
Nonfatal MI[c]	*0.91 (0.73–1.14)*	*40*	*43*
CHD death[c]	*1.01 (0.71–1.43)*	*16*	*16*
All strokes[c]	1.33 (1.05–1.68)	45	33
Ischemic stroke[c]	*1.55 (1.19–2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06–2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90–2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62–1.04)	28	34
Colorectal cancer[e]	1.08 (0.75–1.55)	17	16
Hip fracture[c]	0.65 (0.45–0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44–0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47–0.72)	35	59
Total fractures[c,d]	0.71 (0.64–0.80)	144	197
Death due to other causes[e,f]	1.08 (0.88–1.32)	53	50
Overall mortality[c,d]	1.04 (0.88–1.22)	79	75
Global Index[g]	1.02 (0.92–1.13)	206	201

[a]Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b]Nominal CI unadjusted for multiple looks and multiple comparisons.
[c]Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[d]Not included in "global index".
[e]Results are based on an average follow-up of 6.8 years.
[f]All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
[g]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, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures[9]. The absolute excess risk of events included in the "global index" was a nonsignificant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years (see Table 8).

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess was present in all subgroups of women examined[10] (see Table 8).

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50 to 59 years of age, a nonsignificant trend toward reduced risk for CHD [HR 0.63 (95 percent, CI 0.36 to 1.09)] and overall mortality [HR 0.71 (95 percent CI, 0.46 to 1.11)].

Women's Health Initiative Memory Study

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years of age; 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21 to 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**)

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83 to 2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**)

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19 to 2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**)

INDICATIONS AND USAGE

CombiPatch is indicated in a woman with a uterus for:

- Treatment of moderate to severe vasomotor symptoms due to menopause.
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

CONTRAINDICATIONS

CombiPatch is contraindicated in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of breast cancer.
3. Known or suspected estrogen-dependent neoplasia.
4. Active DVT, PE, or history of these conditions.
5. Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions.
6. Known anaphylactic reaction or angioedema or hypersensitivity with CombiPatch.
7. Known liver impairment or disease.
8. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
9. Known or suspected pregnancy.

WARNINGS

See **BOXED WARNING**.

1. Cardiovascular Disorders

An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. An increased risk of stroke and DVT has been reported with estrogen-alone therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

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

a. Stroke

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years). (See **CLINICAL STUDIES**) The increase in risk was demonstrated after the first year and persisted.[1]

Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). (See **CLINICAL STUDIES**) The increase in risk was demonstrated in year 1 and persisted. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

b. Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events (defined as nonfatal MI, silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 (See **CLINICAL STUDIES**).

In the WHI estrogen-alone substudy, no overall effect on CHD events was reported in women receiving estrogen-alone compared to placebo.[2] (See **CLINICAL STUDIES**)

Subgroup analyses of women 50 to 59 years of age suggest a statistically nonsignificant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In postmenopausal women with documented heart disease (n=2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established CHD. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred twenty-one (2,321) 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 plus MPA group and the placebo group in the HERS, the HERS II, and overall.

c. Venous Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and PE) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted.[3] (See **CLINICAL STUDIES**) Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, the risk of VTE was reported to be increased for women receiving daily CE (0.625 mg)-alone compared to women receiving placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women years). The increase in VTE risk was demonstrated during the first 2 years.[4] (See **CLINICAL**

STUDIES) Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

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

2. Malignant Neoplasms

a. Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo.[6] 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 plus 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 plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the 2 groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups.[5] (See **CLINICAL STUDIES**)

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of CE (0.625)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80).[6] (See **CLINICAL STUDIES**)

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and 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 healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

b. Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among users of unopposed estrogen is

about 2 to 12 times greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use with increased risks of 15- to 24-fold for 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 using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital 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.

c. Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically nonsignificant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI 0.77 to 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies and some report no association.

3. Probable Dementia

In the WHIMS estrogen plus progestin ancillary substudy of WHI, a population of 4,532 generally healthy postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21 to 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years.[8] (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**)

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83 to 2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years.[8] (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**)

When data from the 2 populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19 to 2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women.[8] (See **PRECAUTIONS, Geriatric Use)**

4. Gallbladder Disease

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

5. Hypercalcemia

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

6. Visual Abnormalities

Retinal vascular thrombosis has been reported in women 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.

7. Angioedema

Angioedema involving eye/eyelid, face, larynx, pharynx, tongue and extremity (hands, legs, ankles, and fingers) with or without urticaria requiring medical intervention has occurred in the postmarketing experience of using CombiPatch. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Women who develop angioedema anytime during the course of treatment with CombiPatch should not receive it again. Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

8. Severe Anaphylactic/Anaphylactoid Reactions

Cases of anaphylactic/anaphylactoid reactions, which developed anytime during the course of CombiPatch treatment and required emergency medical management, have been reported in the postmarketing setting. Involvement of skin (hives, pruritus, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) has been noted.

PRECAUTIONS

A. General

1. Addition of a Progestin when a Woman has not had a Hysterectomy

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

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

2. Elevated Blood Pressure

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

3. Hypertriglyceridemia

In women with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

4. Hepatic Impairment and/or Past History of Cholestatic Jaundice

Although transdermally administered estrogen therapy avoids first-pass hepatic metabolism, estrogens may be poorly metabolized in women with impaired liver function. For women 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.

5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid Retention

Estrogens plus progestins may cause some degree of fluid retention. Women with conditions which might be influenced by this factor, such as cardiac or renal impairment warrant careful observation when estrogens plus progestins are prescribed.

7. Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

8. Exacerbation of Endometriosis

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

9. Exacerbation of Other Conditions

Estrogen therapy 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.

B. Patient Information

Physicians are advised to discuss the content of the **PATIENT INFORMATION** leaflet and **INSTRUCTIONS FOR USE** with patients for whom they prescribe CombiPatch.

C. Laboratory Tests

Serum FSH and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

Laboratory parameters may be useful in guiding dosage for the treatment of hypoestrogenism due to hypogonadism, castration and primary ovarian failure.

D. Drug-Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex; and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased TBG leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin [CBG], SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma high density lipoprotein (HDL) and HDL-2 subfraction concentrations, reduced low density lipoprotein (LDL) cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

F. Pregnancy

CombiPatch should not be used during pregnancy. (See **CONTRAINDICATIONS.**) There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

G. Nursing Mothers

CombiPatch should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens and progestins have been identified in the breast milk of women receiving these drugs. Caution should be exercised when CombiPatch is administered to a nursing woman.

H. Pediatric Use

CombiPatch is not indicated in children. Clinical studies have not been conducted in the pediatric population.

I. Geriatric Use

There have not been sufficient numbers of geriatric women involved in studies utilizing CombiPatch to determine whether those over 65 years of age differ from younger subjects in their response to CombiPatch.

The Women's Health Initiative Studies

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age. (See **CLINICAL STUDIES.**)

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age. (See **CLINICAL STUDIES.**)

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen plus progestin or estrogen-alone when compared to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia.**)

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable 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.

Table 9. All Adverse Reactions Regardless of Relationship Reported at a Frequency of Greater than or Equal to 5 Percent with CombiPatch

	VASOMOTOR SYMPTOM STUDIES		
	CombiPatch 0.05/0.14 mg per day† n=113	**CombiPatch 0.05/0.25 mg per day† 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%

†Represents milligrams of estradiol/NETA delivered daily by each system.

*Application site reactions includes localized bleeding, bruising, burning, discomfort, dryness, eczema, edema, erythema, inflammation, irritation, pain, papules, paresthesia, pruritus, rash, skin discoloration, skin pigmentation, swelling, urticaria, and vesicles.

Table 10. All Adverse Reactions Regardless of Relationship Reported at a Frequency of Greater than or Equal to 5 Percent with CombiPatch

	ENDOMETRIAL HYPERPLASIA STUDIES		
	CombiPatch	**CombiPatch**	**Vivelle**
	0.05/0.14 mg per day† n=325	**0.05/0.25 mg per day† n=312**	**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%

†Represents milligrams of estradiol/NETA delivered daily by each system.

*Application site reactions includes localized bleeding, bruising, burning, discomfort, dryness, eczema, edema, erythema, inflammation, irritation, pain, papules, paresthesia, pruritus, rash, skin discoloration, skin pigmentation, swelling, urticaria, and vesicles.

Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of CombiPatch. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System

Endometrial hyperplasia, endocervical polyp, uterine leiomyomata, fallopian tube cyst, uterine spasms.

Breast

Breast cancer.

Cardiovascular

Hypertension, varicose veins.

Gastrointestinal

Jaundice cholestatic, cholelithiasis, gall bladder disorder, transaminases increased.

Skin
Skin discoloration.

Central Nervous System
Affect lability, libido disorder, migraine, vertigo, paresthesia.

Miscellaneous
Angioedema, hypersensitivity, weight increased.

OVERDOSAGE

Overdosage of estrogen or estrogen plus progestin may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of CombiPatch therapy with institution of appropriate symptomatic care

DOSAGE AND ADMINISTRATION

Generally, when estrogen therapy is prescribed for a postmenopausal woman with a uterus, a progestin should be considered to reduce the risk of endometrial cancer. A woman without a uterus generally does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin. Use of estrogen-alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be reevaluated periodically as clinically appropriate to determine whether treatment is still necessary. Adequate diagnostic measures, such as directed or random endometrial sampling, when indicated, should be undertaken to rule out malignancy in a postmenopausal woman with a uterus with undiagnosed persistent or recurring abnormal genital bleeding.

Initiation of Therapy

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 plus progestin therapy may start therapy with CombiPatch at any time. However, women currently using continuous estrogen or combination estrogen plus 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 plus 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 cm^2) and 0.05 mg estradiol with 0.25 mg NETA per day (16 cm^2). 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

CombiPatch 0.05 mg estradiol/0.14 mg NETA per day (9 cm^2) matrix transdermal system is used for continuous uninterrupted treatment applied twice weekly on the lower abdomen. A new system should be applied to the skin every 3 to 4 days (twice weekly) during a 28-day cycle.

Additionally, a dose of 0.05 mg estradiol/0.25 mg NETA (16 cm^2 system) is available if a greater progestin dose is desired. 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, a 0.05 mg per day (nominal delivery rate) estradiol transdermal system (Vivelle-Dot®) is worn for the first 14 days of a 28-day cycle, replacing the system every 3 to 4 days (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 cm^2) transdermal system should be worn continuously on the lower abdomen. The CombiPatch system should be replaced every 3 to 4 days (twice weekly) during this 14-day period in the 28-day cycle.

Additionally, a dose of 0.05 mg estradiol/0.25 mg NETA (16 cm^2 system) is available if a greater progestin dose is desired. 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 1 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 1 system should be worn at any 1 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 estradiol/NETA transdermal delivery system is available in:

System Size	Nominal Delivery Rate* Estradiol/NETA	Presentation	NDC	Markings
9 cm^2	0.05/0.14 mg per day	8 systems per carton	68968-0514-8	CombiPatch 0.05/0.14 mg per day
		Cartons of 2 patient packs of 8 systems	68968-0514-4	
16 cm^2	0.05/0.25 mg per day	8 systems per carton	68968-0525-8	CombiPatch 0.05/0.25 mg per day
		Cartons of 2 patient packs of 8 systems	68968-0525-4	

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

Storage Conditions

Prior to dispensing to the patient, store refrigerated 2°C to 8°C (36°F to 46°F). After dispensing to the patient, CombiPatch can be stored at room temperature between 20°C to 25°C (66°F to 77°F) for up to 6 months. **For the Pharmacist:** When CombiPatch is dispensed to the patient, place an expiration date on the label. The date should not exceed either 6 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 and Vivelle-Dot are registered trademarks of Novartis Pharmaceuticals Corporation.

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Manufactured by:
Noven Pharmaceuticals Inc.
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Distributed by:
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Miami, FL 33186

For more information call 1-800-455-8070 or visit www.combipatch.com.

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Patient Information

CombiPatch®

(käm-bē `pach)

(estradiol/norethindrone acetate transdermal system)

Read this Patient Information before you start using CombiPatch and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about CombiPatch (a combination of estrogen and progestin hormones)?

- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes, or dementia (decline of brain function).
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia.

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb).
- Using estrogen-alone may increase your chances of getting stroke or blood clots.
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age or older.

You and your healthcare provider should talk regularly about whether you still need treatment with CombiPatch.

What is CombiPatch?

CombiPatch is a prescription medicine patch (Transdermal System) that contains 2 kinds of hormones, estrogen and progestin.

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 get 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 to use estrogens. In other women, symptoms can be more severe.

- **Treat moderate to severe menopausal changes in and around your vagina**

  You and your healthcare provider should talk regularly about whether you still need treatment with CombiPatch to control these problems. If you use CombiPatch only to treat menopausal changes in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

- **Treat certain conditions in women before menopause if their ovaries do not make enough estrogens naturally.**

  You and your healthcare provider should talk regularly about whether you still need treatment with CombiPatch.

Who should not use CombiPatch?

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

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

Do not start using CombiPatch if you:

- **have unusual vaginal bleeding**

  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **currently have or have had certain cancers**

  Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your health care provider about whether you should use CombiPatch.
- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **have been diagnosed with a bleeding disorder**
- **are allergic to CombiPatch or any of its ingredients**

  See the list of ingredients in CombiPatch at the end of this leaflet.
- **think you may be pregnant**

  CombiPatch is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not use CombiPatch if the test result is positive and talk to your healthcare provider.

What should I tell my healthcare provider before I use CombiPatch?

Before you use CombiPatch, tell your healthcare provider if you:

- **have any unusual vaginal bleeding**

  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **have any other medical conditions**

  Your healthcare provider may need to check you more carefully if you have certain conditions such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face and tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **are going to have surgery or will be on bed rest**

  Your healthcare provider will let you know if you need to stop using CombiPatch.

- **are breastfeeding**

  The hormones in CombiPatch can pass into your breast milk.

Tell your healthcare provider 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. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get new medicine.

How should I use CombiPatch?

- **For detailed instructions, see the step-by-step instructions for using CombiPatch at the end of this Patient Information.**
- Use CombiPatch exactly as your healthcare provider tells you to use it.
- CombiPatch is for skin use only.
- Change your CombiPatch 2 times each week or every 3 to 4 days.
- Apply your CombiPatch to a clean, dry area on your lower abdomen. This area must be clean, dry, and free of powder, oil or lotion for your CombiPatch to stick to your skin.
- Apply your CombiPatch to a different area of your lower abdomen each time. Do not use the same application site 2 times in the same week.
- Do not apply CombiPatch to or near your breasts.
- If you forget to apply a new CombiPatch, you should apply a new CombiPatch as soon as possible.
- Once in place, the transdermal system should not be exposed to the sun for prolonged periods of time.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about your dose and whether you still need treatment with CombiPatch.

How do I change CombiPatch?

- When changing CombiPatch, slowly peel away the used CombiPatch from your skin.
- After you remove CombiPatch, you may have a small amount of stickiness (adhesive) left on your skin. If you have any adhesive left on your skin after you remove CombiPatch, allow the area to dry for 15 minutes. Gently rub the sticky area of your skin with oil or lotion to remove the adhesive.
- **The new CombiPatch must be applied to a different area of your lower abdomen.** This area must be clean, dry, cool and free of powder, oil or lotion. The same site should not be used again for at least 1 week after removal of CombiPatch.

What are the possible side effects of CombiPatch?

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- heart attack
- stroke
- blood clots
- dementia
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- high blood pressure
- high blood sugar
- gallbladder disease
- liver problems
- changes in your thyroid hormone levels
- enlargement of benign tumors of the uterus (“fibroids”)
- depression

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- new breast lumps
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue

Less serious, but common side effects include:

- headache
- breast pain
- irregular vaginal bleeding or spotting
- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection
- redness or irritation at patch placement site

These are not all the possible side effects of CombiPatch. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effects that bother you or does not go away.

You may report side effects to Noven at 1-800-455-8070 or to FDA at 1-800-FDA-1088.

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

- Talk with your healthcare provider regularly about whether you should continue using CombiPatch.
- See your healthcare provider right away if you get vaginal bleeding while using CombiPatch.
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare 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 healthcare provider for ways to lower your chances for getting heart disease.

How should I store and throw away used CombiPatch?

- Store CombiPatch at room temperature between 68ºF to 77ºF (20ºC to 25ºC) for up to 6 months.
- Do not store CombiPatch outside of its pouch.
- Apply immediately upon removal from the protective pouch.
- Used patches still contain estrogen and progestin. To throw away the patch, fold the sticky side of the patch together, place in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet.

Keep CombiPatch and all medicines out of the reach of children.

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.

This leaflet provides a summary of the most important information about CombiPatch. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about CombiPatch that is written for health professionals. You can get more information by calling 1-800-455-8070

What are the ingredients in CombiPatch?

Active Ingredients: estradiol and norethindrone acetate

Inactive Ingredients: acrylic adhesive, silicone adhesive, oleic acid NF, povidone USP, dipropylene glycol, polyester release protective liner and a translucent polyolefin film backing

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Instructions for Use

CombiPatch
(käm-bē `pach)

(estradiol/norethindrone acetate transdermal system)

Step 1. Pick the days you will change your CombiPatch.

- You will need to change your patch every 3 to 4 days (twice weekly).

Step 2. Remove CombiPatch from the pouch.

- Tear open the protective pouch at the slit (do not use scissors) and remove the patch. **See Figure A.**
- The pouch should not be opened until you are ready to put the patch on.

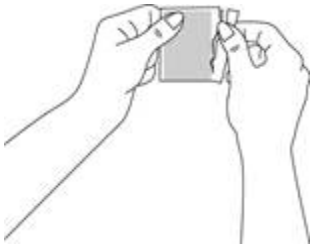

Figure A

Step 3. Remove the adhesive liner.

- Peel off one side of the protective liner. **See Figure B.**
- Do not touch the sticky part of the patch with your fingers. **See Figure B.**

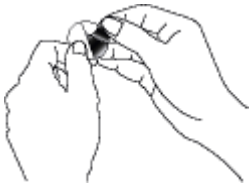

Figure B

Step 4. Placing the CombiPatch on your skin.

- Put the sticky side of the patch on the lower abdomen (below the panty line). **See Figure C.**
- Peel off the second side of the protective liner. **See Figure C.**
- Press the patch firmly in place with your hand for about 10 seconds. **See Figure D.**

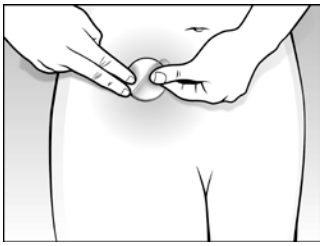

Figure C

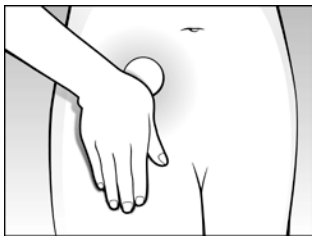

Figure D

Note:

- Avoid the waistline, since clothing and belts may cause the CombiPatch to be rubbed off.
- **Do not apply the CombiPatch to or near your breasts.**
- Only apply the CombiPatch to skin that is clean, dry, and free of any powder, oil, or lotion.
- You should not apply the CombiPatch to injured, burned, or irritated skin, or areas with skin conditions (such as birth marks, tattoos, or that is very hairy).

Step 5. Press the CombiPatch firmly onto your skin.

- Rub the edges of the CombiPatch with your fingers to make sure that it will stick to your skin. **See Figure E.**

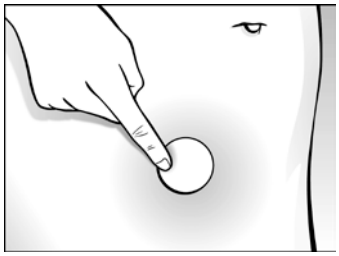

Figure E

Note:

- Bathing, swimming, or showering will not affect the CombiPatch.
- Once in place, the patch should not be exposed to the sun for prolonged periods of time.
- If your CombiPatch falls off reapply it. If you cannot reapply the CombiPatch, apply a new CombiPatch to another area **(See Figures C, D and E)** and continue to follow your original placement schedule.
- If you stop using your CombiPatch or forget to apply a new CombiPatch as scheduled you may have spotting, or bleeding, and your symptoms may come back.

Step 6. Throwing away your used CombiPatch.

- When it is time to change your CombiPatch, remove the old CombiPatch before you apply a new one.

- To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

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