

CombiPatch®
(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 embol, 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® (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 ¹ (mg) | Nominal Delivery Rate ² (mg per day) Estradiol/NETA |
|----------------|----------------|------------------------|--|
| 9 sq cm round | 0.62 | 2.7 | 0.05/0.14 |
| 16 sq cm round | 0.51 | 4.8 | 0.05/0.25 |

¹ NETA = norethindrone acetate.
² Based on *in vivo/in vitro* flux data, delivery of both components per day via skin of average permeability (interindividual variation in skin permeability is approximately 20%).

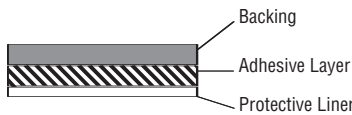
Estradiol USP (estradiol) is a white to creamy white, odorless, crystalline powder, chemically described as estr-1,3,5(10)-triene-3,17β-diol. The molecular weight of estradiol is 272.39 and the molecular formula is C₁₈H₂₄O₂.

Norethindrone acetate USP is a white to creamy white, odorless, crystalline powder, chemically described as 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate. The molecular weight of norethindrone acetate is 340.47 and the molecular formula is C₂₂H₂₈O₃.

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, the 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, polyvidone 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 estrone. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 10 to 500 mg 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 level 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 after routine 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) | | | | |
|---|----------------------------------|------------------|------------------|------------------|
| Estradiol | | | | |
| System Size | Dose Estradiol/NETA (mg per day) | C _{max} | C _{min} | C _{avg} |
| 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 (19) |
| Estrone | | | | |
| 9 sq cm | 0.05/0.14 | 72 (23) | 49 (19) | 54 (21) |
| 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 | | | | |
|--|------------------|------------------|------------------|-----------|
| Dose Estradiol/NETA (mg per day) | | | | |
| System Size | C _{max} | C _{min} | C _{avg} | |
| 9 sq cm | 0.05/0.14 | 617 (341) | 386 (137) | 489 (244) |
| 16 sq cm | 0.05/0.25 | 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 estrone, 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 estrone 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, ketconazole, 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® 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 flashes 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 flashes (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 Flashes and Daily Intensity of Hot Flashes per Day in CombiPatch® Continuous Combined Transdermal Therapy | | |
|---|---|-------------------|-------------------|
| | CombiPatch® Continuous Combined | Placebo | |
| 0.05/0.14 mg per day ¹ | 0.05/0.25 mg per day ² | | |
| Adjusted Mean Change from Baseline ¹ | n=57 | n=52 | n=51 |
| Number of Hot Flashes ³ | -9.3 ⁴ | -8.9 ⁴ | -6.2 |
| Daily Intensity of Hot Flashes ^{4,5} | -4.6 ^{6,6} | -5.0 ⁶ | -2.8 ⁶ |

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

| | Adjusted Mean Change in the Number of Hot Flashes and Daily Intensity of Hot Flashes per Day in CombiPatch® Continuous Sequential Transdermal Therapy | | |
|---|---|-------------------|------|
| | CombiPatch® Continuous Sequential | Placebo | |
| 0.05/0.14 mg per day ¹ | 0.05/0.25 mg per day ² | | |
| Adjusted Mean Change from Baseline ¹ | n=54 | n=59 | n=53 |
| Number of Hot Flashes ³ | -9.3 ⁴ | -9.5 ⁴ | -5.5 |
| Daily Intensity of Hot Flashes ^{4,5} | -4.4 ⁶ | -4.5 ⁶ | -2.1 |

¹ Means were adjusted for imbalance among treatment groups and investigators (least squares mean from ANOVA).
² Represents the milligrams of estradiol/norethindrone acetate delivered daily by each system.
³ Population represents those patients who had baseline and endpoint observations.
⁴ The intensity of hot flashes 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 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 | | |
|--|---|---------------------|-----|
| | CombiPatch® Continuous Combined | Vivelle® Continuous | |
| 0.05/0.14 mg per day ¹ | 0.05/0.25 mg per day ² | 0.05 mg per day | |
| No. of Patients with Biopsies ² | 123 | 98 | 103 |

No. (%) of Patients with Hyperplasia

| | | |
|----------------------|---------------------|-----------------------|
| 1 (<1%) ³ | 1 (1%) ⁴ | 39 (38%) ⁵ |
|----------------------|---------------------|-----------------------|

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

| | Incidence of Endometrial Hyperplasia in a Continuous Sequential CombiPatch® Regimen | | |
|--|---|---------------------|-----|
| | CombiPatch® Continuous Sequential | Vivelle® Continuous | |
| 0.05/0.14 mg per day ¹ | 0.05/0.25 mg per day ² | 0.05 mg per day | |
| No. of Patients with Biopsies ² | 117 | 114 | 115 |

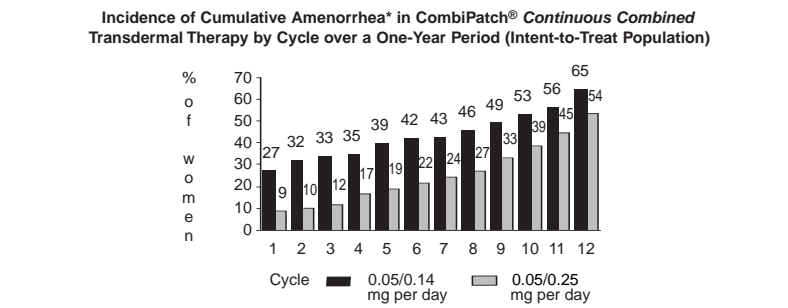
No. (%) of Patients with Hyperplasia

| | | |
|------------------------|------------------------|----------|
| 1 (<1%) ^{3,4} | 1 (<1%) ^{3,5} | 23 (20%) |
|------------------------|------------------------|----------|

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

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 cycle 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.



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

Information Regarding Lipid Effects

The results of clinical trials conducted in a 90% Caucasian population at low risk for cardiovascular disease showed that compared to Vivelle (an estrogen-alone treatment), CombiPatch demonstrated significantly greater reductions in total cholesterol (TC) concentrations. Mean high density lipoprotein-cholesterol (HDL-C) values, however, decreased after one year of CombiPatch therapy whereas they were noted to increase in Vivelle users. Shifts in mean TC/HDL-C were minimal after one year of therapy in both Vivelle and CombiPatch treatment groups. Decreases in triglycerides were observed in both CombiPatch 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 Parameter (%) | CombiPatch® Continuous Combined | | Vivelle® Continuous |
|---------------------|-----------------------------------|-----------------------------------|---------------------|
| | 0.05/0.14 mg per day ¹ | 0.05/0.25 mg per day ² | 0.05 mg per day |
| Total Cholesterol | -5.4% ² | -8.6% ² | -2.0% ² |
| HDL-C | -3.1% ² | -9.1% ² | +7.3% ² |
| LDL-C | -4.6% ² | -7.6% ² | -3.4% ² |
| Triglycerides | -4.6% ² | -9.5% ² | -6.7% ² |

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

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

| Lipid Parameter (%) | CombiPatch® Continuous Sequential | | Vivelle® Continuous |
|---------------------|-----------------------------------|-----------------------------------|---------------------|
| | 0.05/0.14 mg per day ¹ | 0.05/0.25 mg per day ¹ | 0.05 mg per day |
| Total Cholesterol | -4.1% ² | -9.0% ² | -1.0% ² |
| HDL-C | -4.7% ² | -8.9% ² | +0.9% ² |
| LDL-C | -2.9% ² | -6.8% ² | -2.0% ² |
| Triglycerides | -8.2% ² | -14.1% ² | +13.2% ² |

¹ Represents milligrams of estradiol/NETA delivered daily by each system.
² Comparison with estradiol-only patch was significant (p <0.05).
³ Comparison with estradiol-only patch was significant (p <0.001).
⁴ Total number of patients with available data is 114.
⁵ Total number of patients with available data is 110.
⁶ 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.

| Event ^c | Table III. Relative and Absolute Risk Seen in the CE/MPA Substudy of WHI ^a | | |
|---|---|--|---|
| | Relative Risk CE/MPA vs. Placebo at 5.2 Years ^b (95% CI) ^d | Placebo Absolute Risk per 10,000 Women-Years | CE/MPA 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 ^e | 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 ^c | 1.15 (1.03-1.28) | 151 | 170 |
| Deep Vein Thrombosis ^f | 2.07 (1.49-2.87) | 13 | 26 |
| Vertebral Fractures ^g | 0.66 (0.44-0.98) | 15 | 9 |
| Other Osteoporotic Fractures ^h | 0.77 (0.69-0.86) | 170 | 131 |

^a Adapted from JAMA, 2002; 288: 321-333.
^b Includes metastatic and non-metastatic breast cancer with the exception of *in situ* breast cancer.
^c A subset of the events was compared 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.
^d Not included in global index.
^e 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

| | | | |
|--|------------|------------|------------|
| 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% |

¹Represents 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.

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® estradiol/norethindrone acetate transdermal delivery system is available in:

| System Size | Nominal Delivery Rate* Estradiol/Norethindrone Acetate | Presentation | NDC | Markings |
|-------------|---|---|--------------|---------------------------------|
| 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 of 8 systems | 0078-0377-45 | |
| 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® is a registered trademark of Novartis Pharmaceuticals Corporation.

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T2005-16

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)? |
|---|
| <ul style="list-style-type: none"> Do not use estrogens and progestins to prevent heart disease, heart attacks, strokes, or dementia. |
| <p>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.</p> |

What is CombiPatch?

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

CombiPatch is available in two round sizes:

| System Size | Amount of Each Drug in Each System Estradiol/NETA (mg) | Amount of Each Drug Released Every Day Estradiol/NETA (mg per day) |
|-------------|---|---|
| 9 sq cm | 0.05/0.14 | 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?

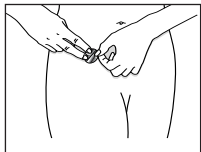
- Put on a new CombiPatch every 3 to 4 days, according to your health care provider's instructions.
- Wear the patch all the time until it is time to replace it with a new patch.
- Change the patch on the same days each week. Your CombiPatch package contains a calendar checklist to help you remember 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.

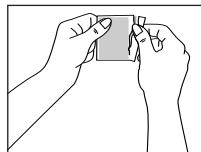


Every time you put on a new CombiPatch, move to a different area on your lower abdomen than used before. The same area should not be used again for at least 1 week.

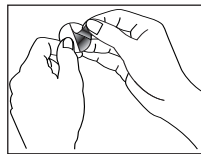
Do not put CombiPatch on or near your breasts. You should not put CombiPatch on the waistline, since tight clothing may rub off the patch. To avoid disturbing the patch it may help to choose an area where your underwear will cover it all the time.

How do you apply CombiPatch?

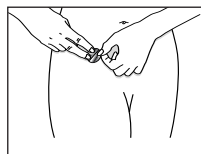
Each CombiPatch is sealed in its own protective pouch. Tear open this pouch at the slit (do not use scissors) and remove the patch. The pouch should not be opened until you are ready to put the patch on.



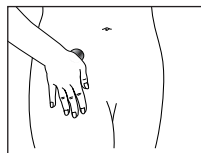
- A protective liner covers the adhesive side of the patch. Peel off one side of the protective liner. Do not touch the sticky part of the patch with your fingers.



- 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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101932-6

CombiPatch®


(estradiol/norethindrone acetate transdermal system)



101932-6

CombiPatch®

(estradiol/norethindrone acetate transdermal system)

| | | | |
|---|--------------|---------------|------------------------|
|  NOVARTIS | | | Ready for Press |
| Product | CombiPatch | Colors | Date: |
| Noven ID. No. | 101932-6 | text | |
| Novartis Code No. | | Black | |
| Description | PI/PPI | text | Signatures: |
| Dimension | 22 x 16.5 | Novartis Logo | |
| Country | USA | Black | |
| Die Line No. | XXXX | Strength | |
| Receiving Plant | East Hanover | Product Logo | |
| | | Black | |