HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CLIMARA safely and effectively. See full prescribing information for CLIMARA.

Climara® (estradiol transdermal system)
Initial U.S. Approval: 1975

WARNING: CARDIOVASCULAR DISORDERS, ENDOMETRIAL CANCER, BREAST CANCER and PROBABLE DEMENTIA
See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.1)**
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism, and myocardial infarction (5.1)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Malignant Neoplasms (5.2) 11/2017

---------- INDICATIONS AND USAGE----------

Climara is an estrogen indicated for:

- Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause (1.1)
- Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause (1.2)
- Treatment of Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure (1.3)
- Prevention of Postmenopausal Osteoporosis (1.4)

----------DOSAGE AND ADMINISTRATION----------

- Start therapy with Climara 0.025 mg per day applied to the skin once-weekly. Dosage adjustment should be guided by the clinical response (2.1)
- Climara should be placed on a clean, dry area of the lower abdomen (below the umbilicus) or upper quadrant of the buttock. Climara should not be applied to the breasts (2.5)

---------- DOSAGE FORMS AND STRENGTHS----------

- Transdermal system 0.025 mg per day, 0.0375 mg per day, 0.05 mg per day, 0.06 mg per day, 0.075 mg per day and 0.1 mg per day (3)

---------- CONTRAINDICATIONS ----------

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.2)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema with Climara (4)
- Known liver impairment or disease (4, 5.10)
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

---------- WARNINGS AND PRECAUTIONS ----------

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogens if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid hormone replacement therapy (5.11, 5.18)

---------- ADVERSE REACTIONS ----------

In a prospective, randomized, placebo-controlled, double-blind study, the most common adverse reactions (≥10 percent) are breast pain, upper respiratory tract infections, headaches, abdominal pain, pain, and edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-84-BAYER (1-888-842-2937) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS----------

- Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the WHIMS ancillary studies of the WHI (5.3, 8.5, 14.4)

See 17 **for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**

Revised: 11/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA
1 INDICATIONS AND USAGE
1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause
1.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause
1.3 Treatment of Hypoestrogenism due to Hypogonadism, Castration, or Primary Ovarian Failure
1.4 Prevention of Postmenopausal Osteoporosis
2 DOSAGE AND ADMINISTRATION
2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause
2.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause
2.3 Treatment of Hypoestrogenism due to Hypogonadism, Castration, or Primary Ovarian Failure
2.4 Prevention of Postmenopausal Osteoporosis
2.5 Application of the Climara Transdermal System
2.6 Removal of the Climara Transdermal System
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Cardiovascular Disorders
5.2 Malignant Neoplasms
5.3 Probable Dementia
5.4 Gallbladder Disease
5.5 Hypercalcemia
5.6 Visual Abnormalities
5.7 Addition of a Progestin When a Woman Has Not Had a Hysterectomy
5.8 Elevated Blood Pressure

Reference ID: 4175150

5.9 Hypertriglyceridemia
5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice
5.11 Hypothyroidism
5.12 Fluid Retention
5.13 Hypocalcemia
5.14 Exacerbation of Endometriosis
5.15 Hereditary Angioedema
5.16 Exacerbation of Other Conditions
5.17 Laboratory Tests
5.18 Drug-Laboratory Test Interactions
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Metabolic Interactions
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment Of Fertility
14 CLINICAL STUDIES
14.1 Effects on Vasomotor Symptoms
14.2 Effects on Bone Mineral Density
14.3 Women's Health Initiative Studies
14.4 Women's Health Initiative Memory Study
15 REFERENCES
16. HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

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

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 and Precautions (5.2)]*.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.3, 14.4)]*.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.3)]*.

The WHI Memory Study (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 Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Reference ID: 4175150

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

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.3, 14.4)]*.

The WHI estrogen plus progestin substudy reported increased risks of 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 CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.3)]*.

The 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 Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.2), and Clinical Studies (14.3)]*.

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.

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

1.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

Limitation of Use

When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, topical vaginal products should be considered.

1.3 Treatment of Hypoestrogenism due to Hypogonadism, Castration, or Primary Ovarian Failure

1.4 Prevention of Postmenopausal Osteoporosis

Limitation of Use

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medication should be carefully considered.

2 DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer. A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.2, 5.14)]*.

Reference ID: 4175150

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 re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Start therapy with 0.025 mg per day applied to the skin once weekly. Therapy should be started at the lowest effective dose and the shortest duration consistent with the treatment goals. Attempts to taper or discontinue the medication should be made at 3 to 6 month intervals.

2.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

Start therapy with 0.025 mg per day applied to the skin once weekly. Therapy should be started at the lowest effective dose and the shortest duration consistent with the treatment goals. Attempts to taper or discontinue the medication should be made at 3 to 6 month intervals.

2.3 Treatment of Hypoestrogenism due to Hypogonadism, Castration, or Primary Ovarian Failure

Start therapy with 0.025 mg per day applied to the skin once weekly. The dose should be adjusted as necessary to control symptoms. Clinical responses (relief of symptoms) at the lowest effective dose should be the guide for establishing administration of the Climara transdermal system, especially in women with an intact uterus.

2.4 Prevention of Postmenopausal Osteoporosis

Start therapy with 0.025 mg per day applied to the skin once weekly.

2.5 Application of the Climara Transdermal System

Site Selection

- The adhesive side of Climara should be placed on a clean, dry area of the lower abdomen or the upper quadrant of the buttock.
- Climara should not be applied to or near the breasts.
- The sites of application must be rotated, with an interval of at least 1-week allowed between applications to the same site.
- The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the transdermal system off.
- Application to areas where sitting would dislodge Climara should also be avoided.

Application

- Climara should be applied immediately after opening the pouch and removing the protective liner.
- Climara should be pressed firmly in place with the fingers for at least 10 seconds, making sure there is good contact, especially around the edges.
- If the system lifts, apply pressure to maintain adhesion.
- In the event that a system should fall off reapply it to a different location. If the system cannot be reapplied, a new system should be applied for the remainder of the 7-day dosing interval.
- Only one system should be worn at any one time during the 7-day dosing interval.
- Swimming, bathing, or using a sauna while using Climara has not been studied, and these activities may decrease the adhesion of the system and the delivery of estradiol.

2.6 Removal of the Climara Transdermal System

- Removal of Climara should be done carefully and slowly to avoid irritation of the skin.
- Should any adhesive remain on the skin after removal of the Climara system, allow the area to dry for 15 minutes. Then gently rubbing the area with an oil-based cream or lotion should remove the adhesive residue.

Reference ID: 4175150

- Used patches still contain some active hormones. Each patch should be carefully folded in half so that it sticks to itself before throwing it away.

3 DOSAGE FORMS AND STRENGTHS

- Climara (estradiol transdermal system), 0.025 mg per day—each 6.5 cm^2 system contains 2 mg of estradiol
- Climara (estradiol transdermal system), 0.0375 mg per day—each 9.375 cm^2 system contains 2.85 mg of estradiol
- Climara (estradiol transdermal system), 0.05 mg per day—each 12.5 cm^2 system contains 3.8 mg of estradiol
- Climara (estradiol transdermal system), 0.060 mg per day—each 15 cm^2 system contains 4.55 mg of estradiol
- Climara (estradiol transdermal system), 0.075 mg per day—each 18.75 cm^2 system contains 5.7 mg of estradiol
- Climara (estradiol transdermal system), 0.1 mg per day—each 25.0 cm^2 system contains 7.6 mg of estradiol

4 CONTRAINDICATIONS

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

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or a history of these conditions
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
- Known anaphylactic reaction or angioedema with Climara
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin 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.

Stroke

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). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.3)]*. 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]

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 (14.3)]*. The increase in risk was demonstrated after

Reference ID: 4175150

the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.3)]*.

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

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events 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 (14.3)]*.

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 coronary heart disease. 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. A total of 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 HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to 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[3] *[see Clinical Studies(14.3)]*. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving 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[4] *[see Clinical Studies(14.3)]*. Should a VTE occur or be suspected, estrogen plus progestin 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.

5.2 Malignant Neoplasms

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 unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with 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. 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.

Reference ID: 4175150

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 in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-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]*[5] *[see Clinical Studies (14.3)]*.

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. 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 *[see Clinical Studies (14.3)]*. 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 two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[6] *[see Clinical Studies (14.3)]*.

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 generally 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.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant 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, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years]vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27 to 1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

Reference ID: 4175150

5.3 Probable Dementia

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, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 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 of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

When data from the two 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, 1.19-2.60). 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 Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

5.4 Gallbladder Disease

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

5.5 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women 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.

5.6 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.

5.7 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.

5.8 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 estrogens on blood pressure was not seen.

5.9 Hypertriglyceridemia

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

5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice

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.

Reference ID: 4175150

5.11 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.

5.12 Fluid Retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal impairment, warrant careful observation when estrogen-alone is prescribed.

5.13 Hypocalcemia

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

5.14 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.

5.15 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

5.16 Exacerbation of Other Conditions

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

5.17 Laboratory Tests

Serum follicle stimulating hormone (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.

5.18 Drug-Laboratory Test Interactions

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

Increased TBG levels 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.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total 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-l-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, and increased triglyceride levels.

Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning, and Warnings and Precautions (5.1)]*

Reference ID: 4175150

- Malignant Neoplasms *[see Boxed Warning, and Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect pooled data from 5 clinical trials of Climara. A total of 614 women were exposed to Climara for 3 months (193 women at 0.025 mg per day, 201 women at 0.05 mg per day, 194 women at 0.1 mg per day) in randomized, double-blind trials of clinical efficacy versus placebo and versus active comparator. All women were postmenopausal, had a serum estradiol level of less than 20 pg/mL, and a minimum of five moderate to severe hot flushes per week or a minimum of 15 hot flushes per week of any severity at baseline. Included in this table are an additional 25 postmenopausal hysterectomized women exposed to Climara 0.025 mg per day for 6 to 24 months (N=16 at 24 months) in a randomized, double-blind, placebo-controlled study of Climara for the prevention of osteoporosis.

Table 1: Treatment-Emergent Adverse Reactions Reported at a Frequency of ≥5 Percent and More Frequent in Women Receiving Climara

	Climara			
Body System Adverse Reactions	**0.025 mg/day[a]** **(N=219)**	**0.05 mg/day[b]** **(N=201)**	**0.1 mg/day[b]** **(N=194)**	**Placebo[c]** **(N=72)**
Body as a Whole	21%	39%	37%	29%
Headache	5%	18%	13%	10%
Pain	1%	8%	11%	7%
Back Pain	4%	8%	9%	6%
Edema	0.5%	13%	10%	6%
Digestive System	9%	21%	29%	18%
Abdominal Pain	0%	11%	16%	8%
Nausea	1%	5%	6%	3%
Flatulence	1%	3%	7%	1%
Musculoskeletal System	7%	9%	11%	4%
Arthralgia	1%	5%	5%	3%
Nervous System	13%	10%	11%	1%
Depression	1%	5%	8%	0%
Urogenital System	12%	18%	41%	11%
Breast Pain	5%	8%	29%	4%
Leukorrhea	1%	6%	7%	1%
Respiratory System	15%	26%	29%	14%
URTI	6%	17%	17%	8%
Pharyngitis	0.5%	3%	7%	3%
Sinusitis	4%	4%	5%	3%
Rhinitis	2%	4%	6%	1%
Skin and Appendages	19%	12%	12%	15%
Pruritus	0.5%	6%	3%	6%

a) Adverse reactions occurring at rate of ≥5 percent in Climara trials of clinical efficacy versus placebo and versus active comparator; and trial of Climara versus placebo for the prevention of osteoporosis
b) Adverse reactions occurring at rate of ≥5 percent in Climara trials of clinical efficacy versus placebo and versus active comparator
c) Adverse reactions occurring in placebo group in Climara trial of clinical efficacy versus placebo

6.2 Postmarketing Experience

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

Reference ID: 4175150

Genitourinary System

Changes in bleeding pattern, pelvic pain

Breast

Breast cancer, breast pain, breast tenderness

Cardiovascular

Changes in blood pressure, palpitations, hot flashes

Gastrointestinal

Vomiting, abdominal pain, abdominal distension, nausea

Skin

Alopecia, hyperhidrosis, night sweats, urticaria, rash

Eyes

Visual disturbances, contact lens intolerance,

Central Nervous System

Depression, migraine, paresthesia, dizziness, anxiety, irritability, mood swings, nervousness, insomnia, headache

Miscellaneous

Fatigue, menopausal symptoms, weight increase, application site reaction, anaphylactic reactions

7 DRUG INTERACTIONS

7.1 Metabolic 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 (hypericum perforatum) preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Climara should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as oral contraceptives inadvertently during early pregnancy.

8.3 Nursing Mothers

Climara 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 have been identified in the breast milk of women receiving estrogen therapy. Caution should be exercised when the Climara transdermal system is administered to a nursing woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Reference ID: 4175150

The Women's Health Initiative 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 (14.3)]*.

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 (14.3)]*.

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-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions (5.3), and Clinical Studies (14.4)]*.

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 Warnings and Precautions (5.3), and Clinical Studies (14.4)]*.

8.6 Renal Impairment

In postmenopausal women with end stage renal disease (ESRD) receiving maintenance hemodialysis, total estradiol serum levels are higher than in normal subjects at baseline and following oral doses of estradiol. Therefore, conventional transdermal estradiol doses used in individuals with normal renal function may be excessive for postmenopausal women with ESRD receiving maintenance hemodialysis.

8.7 Hepatic Impairment

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

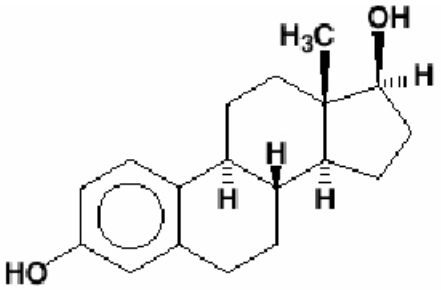
10 OVERDOSAGE

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

11 DESCRIPTION

Climara (estradiol transdermal system), is designed to release estradiol continuously upon application to intact skin. Six (6.5, 9.375, 12.5, 15, 18.75 and 25 cm^2) systems are available to provide nominal *in vivo* delivery of 0.025, 0.0375, 0.05, 0.06, 0.075 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 9.375, 12.5, 15, 18.75 or 25 cm^2, and contains 2, 2.85, 3.8, 4.55, 5.7 or 7.6 mg of estradiol USP respectively. The composition of the systems per unit area is identical.

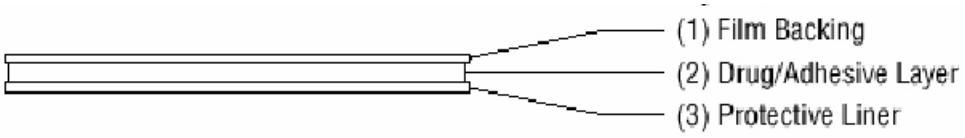
Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3, 17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.38. The structural formula is:



Reference ID: 4175150

The Climara transdermal system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are:

1. A translucent polyethylene film.
2. An acrylate adhesive matrix containing estradiol USP.
3. A protective liner of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the system can be used.



The active component of the transdermal system is estradiol. The remaining components of the transdermal system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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, which is 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, 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 FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

There are no pharmacodynamic data for Climara.

12.3 Pharmacokinetics

Absorption

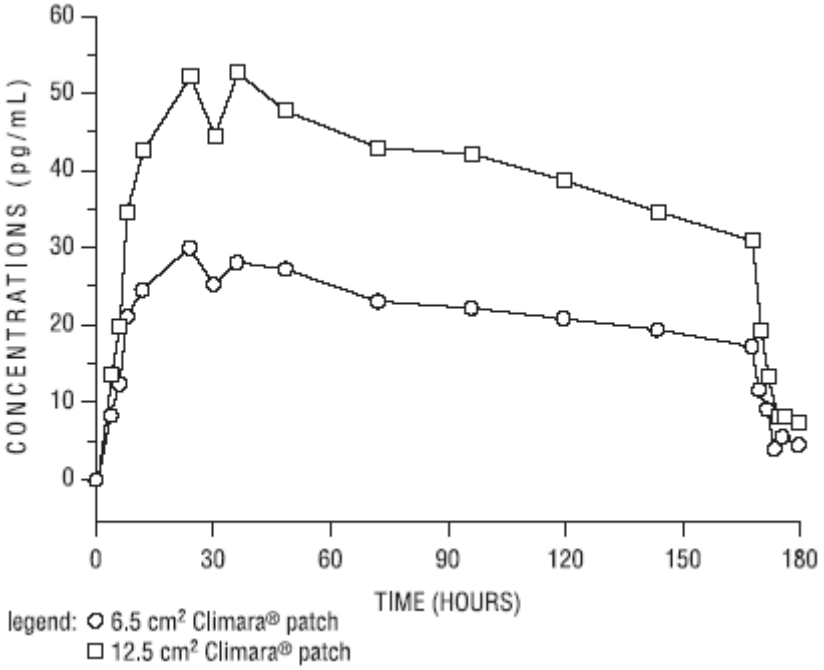
Transdermal administration of Climara produces mean serum concentrations of estradiol comparable to those produced by premenopausal women in the early follicular phase of the ovulatory cycle. The pharmacokinetics of estradiol following application of the Climara transdermal system were investigated in 197 healthy postmenopausal women in six studies. In five of the studies, the Climara transdermal system was applied to the abdomen, and in a sixth study, application to the buttocks and abdomen were compared.

The Climara transdermal delivery system continuously releases estradiol which is transported across intact skin leading to sustained circulating levels of estradiol during a 7-day treatment period. The systemic availability of estradiol after transdermal administration is about 20 times higher than that after oral administration. This difference is due to the absence of first pass metabolism when estradiol is given by the transdermal route.

In a bioavailability study, the Climara 6.5 cm^2 was studied with the Climara 12.5 cm^2 as reference. The mean estradiol levels in serum from the two sizes are shown in Figure 1.

Reference ID: 4175150

Figure 1: Mean Serum 17ß -Estradiol Concentrations versus Time Profile following Application of a 6.5 cm^2 Transdermal System and Application of a 12.5 cm^2 Climara Transdermal System



Dose proportionality was demonstrated for the Climara 6.5 cm^2 transdermal system as compared to the Climara 12.5 cm^2 transdermal system in a 2-week crossover study with a 1-week washout period between the two-transdermal systems in 24 postmenopausal women.

Dose proportionality was also demonstrated for the Climara transdermal system (12.5 cm^2 and 25 cm^2) in a 1-week study conducted in 54 postmenopausal women. The mean steady state levels (C_{avg}) of the estradiol during the application of Climara 25 cm^2 and 12.5 cm^2 on the abdomen were about 80 and 40 pg/mL, respectively.

In a 3-week multiple application study in 24 postmenopausal women, the 25 cm^2 Climara transdermal system produced average peak estradiol concentrations (C_{max}) of approximately 100 pg/mL. Trough values at the end of each wear interval (C_{min}) were approximately 35 pg/mL. Nearly identical serum curves were seen each week, indicating little or no accumulation of estradiol in the body. Serum estrone peak and trough levels were 60 and 40 pg/mL, respectively.

In a single dose, randomized, crossover study conducted to compare the effect of site of application, 38 postmenopausal women wore a single Climara 25 cm^2 transdermal system for 1 week on the abdomen and buttocks. The estradiol serum concentration profiles are shown in Figure 2. Values of C_{max} and C_{avg} were, respectively, 25 percent and 17 percent higher with the buttock application than with the abdomen application.

Reference ID: 4175150

Figure 2: Observed Mean (± SE) Estradiol Serum Concentrations for a One Week Application of the Climara Transdermal System (25 cm^2) to the Abdomen and Buttocks of 38 Postmenopausal Women

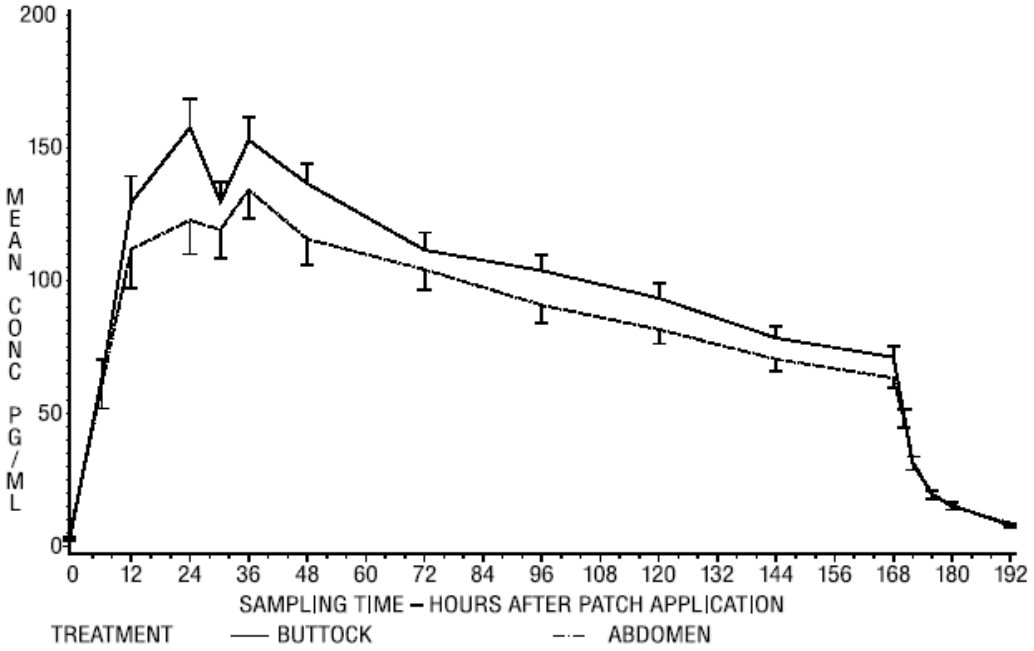


Table 2 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of the Climara transdermal system.

Table 2: Pharmacokinetic Summary (Mean Estradiol Values)

Climara Delivery Rate	Surface Area (cm^2)	Application Site	No. of Subjects	Dosing	C_{max} (pg/mL)	C_{min} (pg/mL)	C_{avg} (pg/mL)
0.025	6.5	Abdomen	24	Single	32	17	22
0.05	12.5	Abdomen	102	Single	71	29	41
0.1	25	Abdomen	139	Single	147	60	87
0.1	25	Buttock	38	Single	174	71	106

The relative standard deviation of each pharmacokinetic parameter after application to the abdomen averaged 50 percent, which is indicative of the considerable intersubject variability associated with transdermal drug delivery. The relative standard deviation of each pharmacokinetic parameter after application to the buttock was lower than that after application to the abdomen (for example, for C_{max} 39 percent versus 62 percent, and for C_{avg} 35 percent versus 48 percent).

Distribution

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 SHBG and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is 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 proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Reference ID: 4175150

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Adhesion

An open-label study of adhesion potentials of placebo transdermal systems that correspond to the 6.5 cm^2 and 12.5 cm^2 sizes of Climara was conducted in 112 healthy women of 45 to 75 years of age. Each woman applied both transdermal systems weekly, on the upper outer abdomen, for 3 consecutive weeks. It should be noted that lower abdomen and upper quadrant of the buttock are the approved sites of application for Climara.

The adhesion assessment was done visually on Days 2, 4, 5, 6, 7 of each week of transdermal system wear. A total of 1,654 adhesion observations were conducted for 333 transdermal systems of each size.

Of these observations, approximately 90 percent showed essentially no lift for both the 6.5 cm^2 and 12.5 cm^2 transdermal systems. Of the total number of transdermal systems applied, approximately 5 percent showed complete detachment for each size. Adhesion potentials of the 18.75 cm^2 and 25 cm^2 sizes of transdermal systems (0.075 mg per day and 0.1 mg per day) have not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms

A study of 214 women 25 to 74 years of age met the qualification criteria and were randomly assigned to one of the three treatment groups: 72 to the 0.05 mg estradiol patch, 70 to the 0.1 mg estradiol patch, and 72 to placebo. Potential subjects were postmenopausal women in good general health who experienced vasomotor symptoms. Natural menopause patients had not menstruated for at least 12 months and surgical menopause patients had undergone bilateral oophorectomy at least 4 weeks before evaluation for study entry. In order to enter the 11-week treatment phase of the study, potential subjects must have experienced a minimum of five moderate to severe hot flushes per week, or a minimum of 15 hot flushes of any severity per week, for 2 consecutive weeks. Women wore the patches in a cyclical fashion (three weeks on and one week off).

During treatment, all subjects used diaries to record the number and severity of hot flushes. Subjects were monitored by clinic visits at the end of weeks 1, 3, 7, and 11 and by telephone at the end of weeks 4, 5, 8, and 9.

Adequate data for the analysis of efficacy was available from 191 subjects. The results are presented as the mean ± SD number of flushes in each of the 3 treatment weeks of each 4-week cycle. In the 0.05 mg estradiol group, the mean weekly hot flush rate across all treatment cycles decreased from 46 ± 6.5 at baseline to 20 ± 3 (-67 percent). The 0.1 mg estradiol group had a decline in the mean weekly hot flush rate from 52 ± 4.4 at baseline to 16 ± 2.4 (-72 percent). In the placebo group, the mean weekly hot flush rate declined from 53 ± 4.5 at baseline to 46 ± 6.5 (-18.1 percent). Compared with placebo, the 0.05 mg and 0.1 mg estradiol groups showed a statistically significantly larger mean decrease in hot flushes across all treatment cycles ($P<0.05$). When the response to treatment was analyzed for each of the three cycles of therapy, similar statistically significant differences were observed between both estradiol treatment groups and the placebo group during all treatment cycles.

In a double-blind, placebo-controlled, randomized study of 187 women receiving Climara 0.025 mg per day or placebo continuously for up to three 28-day cycles, the Climara 0.025 mg per day dosage was shown to be statistically better than placebo at weeks 4 and 12 for relief of both the frequency and severity of moderate to severe vasomotor symptoms.

Reference ID: 4175150

Table 3: Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms Intent to Treat (ITT)

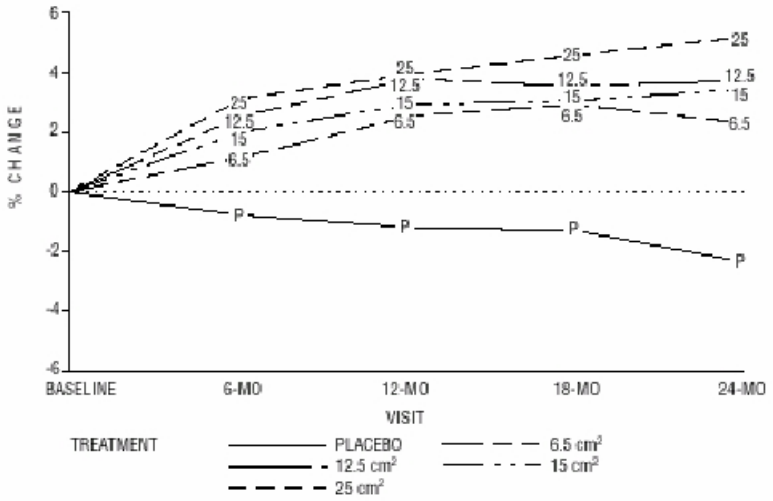
Treatment Group	Statistics	Week 4	Week 8	Week 12
E_2 Transdermal System	N	82	84	68
	Mean	-6.45	-7.69	-7.56
	SD	4.65	4.76	4.64
Placebo	N	83	71	65
	Mean	-5.11	-5.98	-5.98
	SD	7.43	8.63	9.69
	p-value	<0.002		<0.003

A second active-control trial of 193 randomized subjects was supportive of the placebo-controlled trial.

14.2 Effects on Bone Mineral Density

A two-year clinical trial enrolled a total of 175 healthy, hysterectomized, postmenopausal, non-osteoporotic (that is, lumbar spine bone mineral density >0.9 gm/cm^2) women at 10 study centers in the United States. A total of 129 subjects were allocated to receive active treatment with 4 different doses of estradiol patches (6.5, 12.5, 15, 25 cm^2) and 46 subjects were allocated to receive placebo patches. Seventy-seven percent of the randomized subjects (100 on active drug and 34 on placebo) contributed data to the analysis of percent change of anterior-posterior (A-P) spine BMD, the primary efficacy variable (see Figure 3). A statistically significant overall treatment effect at each timepoint was noted, implying bone preservation for all active treatment groups at all timepoints, as opposed to bone loss for placebo at all timepoints.

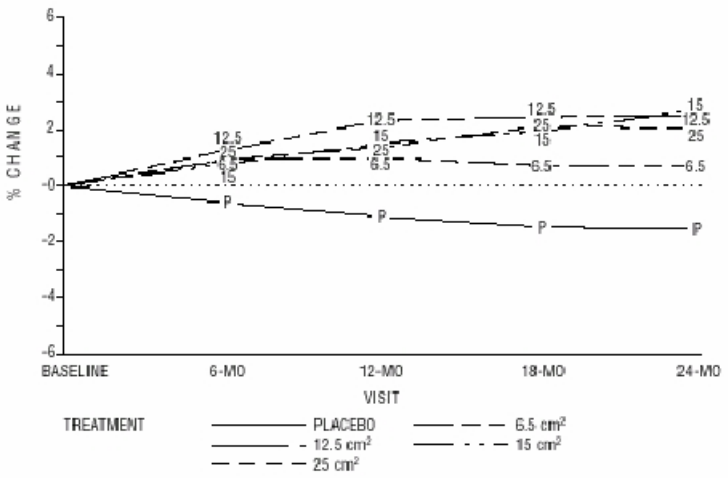
Figure 3: Mean Percent Change from Baseline in Lumbar Spine (A-P View) Bone Mineral Density By Treatment and Time Last Observation Carried Forward



Percent change in BMD of the total hip (see Figure 4) was also statistically significantly different from placebo for all active treatment groups. This figure is based on 74 percent of the randomized subjects (95 on active drug and 34 on placebo).

Reference ID: 4175150

Figure 4 Mean Percent Change from Baseline in Total Hip by Treatment and Time Last Observation Carried Forward



14.3 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 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 causes. These substudies did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms.

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 risk 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: 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 4.

Table 4. 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
Non-fatal 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 (0.9-2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62-1.04)	28	34
Colorectal cancer[c]	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

Reference ID: 4175150

Total fractures[c,d]	0.71 (0.64-0.80)	144	197
Death due to 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 confidence intervals 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, endometrial cancer, 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 risks 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 non-significant 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 4.

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 the distribution of stroke subtype and severity, including fatal strokes, in women receiving estrogen-alone compared to placebo. Estrogen-alone increased the risk of ischemic stroke, and this excess risk was present in all subgroups of women examined.[10] See Table 4.

Timing of initiation of estrogen-alone 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 non-significant trend toward reduced risk for CHD *[hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)]* and overall mortality *[HR 0.71 (95 percent CI, 0.46-1.11)]*.

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 reduction per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.5 percent Black, 5.4 percent Hispanic, 3.9 percent Other), are presented in Table 5 . These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 5 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
Non-fatal MI	*1.28 (1.00-1.63)*	*31*	*25*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*

Reference ID: 4175150

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 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, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

Timing of 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 non-significant trend toward reduced risk for overall mortality *[HR 0.69 (95 percent CI, 0.44-1.07)]*.

14.4 Women's Health Initiative Memory Study

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, 0.83-2.66). 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 the study included Alzheimer’s disease (AD), vascular dementia (VaD) and mixed types (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 and Precautions (5.3), and Use in Specific Populations (8.5)]*.

The WHIMS estrogen plus progestin ancillary study 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; and 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, 1.21-3.48). 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 the study included AD, VaD and mixed types (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 and Precautions (5.3), and Use in Specific Populations (8.5)]*.

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, 1.19-2.60). Differences between groups became apparent in the first year of

Reference ID: 4175150

treatment. It is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

15 REFERENCES

1. Rossouw JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. *JAMA.* 2007;297:1465-1477.
2. Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease. *Arch Int Med.* 2006;166:357-365.
3. Curb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus. *Arch Int Med.* 2006;166:772-780.
4. Cushman M, et al. Estrogen Plus Progestin and Risk of Venous Thrombosis. *JAMA.* 2004;292:1573-1580.
5. Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy. *JAMA.* 2006;295:1647-1657.
6. Chlebowski RT, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. *JAMA.* 2003;289:3234-3253.
7. Anderson GL, et al. Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures. *JAMA.* 2003;290:1739-1748.
8. Shumaker SA, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. *JAMA.* 2004;291:2947-2958.
9. Jackson RD, et al. Effects of Conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. *J Bone Miner Res.* 2006;21:817-828.
10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation.* 2006;113:2425-2434.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Climara (estradiol transdermal system), 0.025 mg per day — each 6.5 cm^2 system contains 2 mg of estradiol USP
Individual Carton of 4 systems NDC 50419-454-04

Climara (estradiol transdermal system), 0.0375 mg per day — each 9.375 cm^2 system contains 2.85 mg of estradiol USP
Individual Carton of 4 systems NDC 50419-456-04

Climara (estradiol transdermal system), 0.05 mg per day — each 12.5 cm^2 system contains 3.8 mg of estradiol USP
Individual Carton of 4 systems NDC 50419-451-04

Climara (estradiol transdermal system), 0.06 mg per day — each 15 cm^2 system contains 4.55 mg of estradiol USP
Individual Carton of 4 systems NDC 50419-459-04

Climara (estradiol transdermal system), 0.075 mg per day — each 18.75 cm^2 system contains 5.7 mg of estradiol USP
Individual Carton of 4 systems NDC 50419-453-04

Climara (estradiol transdermal system), 0.1 mg per day — each 25 cm^2 system contains 7.6 mg of estradiol USP
Individual Carton of 4 systems NDC 50419-452-04

16.2 Storage and Handling

Store at 20°C to 25°C (66°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). Do not store above 86°F (30°C).

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

Reference ID: 4175150

Used transdermal systems still contain active hormone. To discard, fold the sticky side of the transdermal system together, place it in a sturdy child-proof container, and place this container in the trash. Used transdermal systems should not be flushed in the toilet.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Vaginal Bleeding

Inform postmenopausal women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible *[see Warning and Precautions (5.2)]*.

Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including cardiovascular disorders, malignant neoplasms, and probable dementia *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Possible Less Serious but Common Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.

Reference ID: 4175150

Patient Information

Climara (Klī-mâr-uh)

(estradiol transdermal system)

Read this Patient Information before you start using Climara 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 Climara (an estrogen hormone)?

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb). Report any unusual vaginal bleeding right away while you are using Climara. 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.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes, or dementia (decline in brain function).
- Using estrogen-alone may increase your chances of getting strokes or blood clots.
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women age 65 years of age or older.
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia.
- 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 age 65 years of age or older.
- You and your healthcare provider should talk regularly about whether you still need treatment with Climara.

What is Climara?

Climara is a prescription medicine patch (Transdermal System) that contains estradiol (an estrogen hormone).

What is Climara used for?

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

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

  You and your healthcare provider should talk regularly about whether you still need treatment with Climara to control these problems. If you use Climara only to treat your 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 produce enough estrogens naturally**
- **Help reduce your chances of getting osteoporosis (thin weak bones)**

  If you use Climara only to prevent osteoporosis due to menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you still need treatment with Climara.

Who should not use Climara?

Do not start using Climara 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 healthcare provider about whether you should use Climara.

- **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 Climara or any of its ingredients**

  See the list of ingredients in Climara at the end of this leaflet.

- **think you may be pregnant**

  Climara 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 Climara if the test is positive and talk to your healthcare provider.

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

Before you use Climara, 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 Climara.

- **are breastfeeding**

  The hormone in Climara 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 Climara works. Climara may also affect how your 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 Climara? For detailed instructions, see the step-by-step instructions for using Climara at the end of this Patient Information.

- Use Climara exactly as your healthcare provider tells you to use it.
- Climara is for skin use only.
- Change your Climara patch 1 time each week or every 7 days.
- Apply your Climara patch to a clean, dry area on your lower abdomen or buttocks. This area must be clean, dry, and free of powder, oil or lotion for your patch to stick to your skin.
- Apply your Climara patch to a different area of your abdomen or your buttocks each time. Do not use the same application site 2 times in the same week.
- Do not apply Climara to your breasts.
- If you forget to apply a new Climara patch, you should apply a new patch as soon as possible.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about the dose you are using and whether you still need treatment with Climara.

How to Change Climara

- When changing Climara, peel off the used patch slowly from the skin.
- After removal of Climara, people usually have either no adhesive residue or light adhesive residue. If any adhesive residue remains on your skin after removing the patch, allow the area to dry for 15 minutes. Then, gently rub the area with an oil-based cream or lotion to remove the adhesive from your skin.
- Keep in mind**, the new patch must be applied to a different skin area of your abdomen or buttocks.** This area must be clean, dry, and free of powder, oil or lotion. The same site should not be used again for at least 1 week after removal of the patch.

What are the possible side effects of Climara?

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”)

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 tenderness or 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 the patch placement site

These are not all the possible side effects of Climara. 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.

Call your doctor for medical advice about side effects. You may report side effects to Bayer Healthcare Pharmaceuticals at 1-888-842-2937 or to FDA at 1-800-FDA-1088.

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

- Talk with your healthcare provider regularly about whether you should continue using Climara.
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you.
- The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the uterus (womb).
- See your healthcare provider right away if you get vaginal bleeding while using Climara.
- 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 of getting heart disease.

How should I store and throw away used Climara?

- Store Climara at room temperature 68°F to 77°F (20°C to 25°C).
- Do not store Climara patches outside of their pouches. Apply immediately upon removal from the protective pouch.
- Used patches still contain estrogen. 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.

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

General information about the safe and effective use of Climara.

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

This leaflet summarizes the most important information about Climara. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Climara that is written for health professionals.

For more information, go to www.climara.com or call Bayer HealthCare Pharmaceuticals Inc at 1-888-842-2937.

What are the ingredients in Climara?

Active ingredient: estradiol

Inactive ingredient: acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

Instructions for Use

Climara (Klī-mâr-uh)

(estradiol transdermal system)

Read this Patient Information before you start using Climara 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.

You will need the following supplies: See Figure A

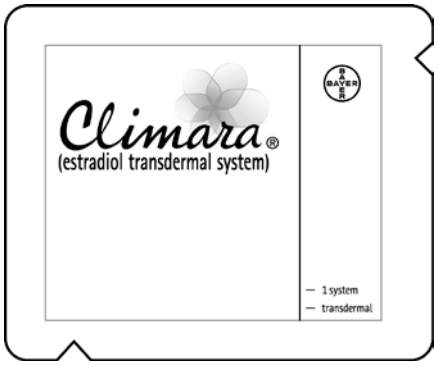


Figure A

Step 1: Pick the days you will change your Climara.

You will need to change your patch 1 time each week or every 7 days.

Step 2. Remove the Climara patch from the pouch.

- Remove patch from its protective pouch by tearing at the notch (do not use scissors). **See Figure B**
- Do not remove your patch from the protective pouch until you are ready to apply it.

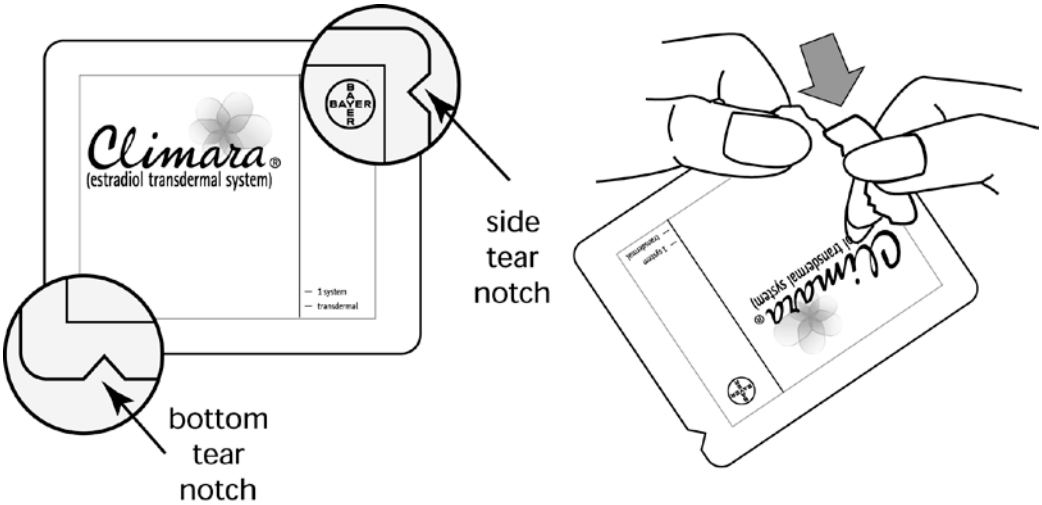


Figure B

Step 3. Remove the adhesive liner. See Figure C

- You will see that Climara is an oval shaped clear patch that is attached to a thick, hard-plastic adhesive liner and covered by a clear, plastic film. **See Figure C**
- To apply your patch you must first remove the protective, clear plastic film that is attached to the clear thicker plastic backing. **See Figure D**
- There is a silver foil-sticker attached to the inside of the pouch. Do not remove the silver foil sticker from the pouch. See Figure E

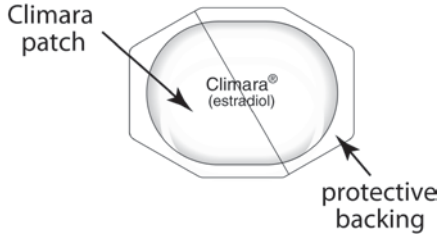


Figure C

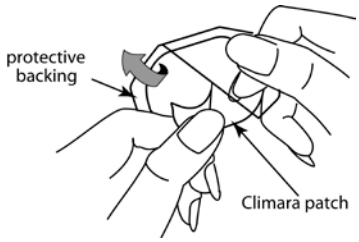


Figure D

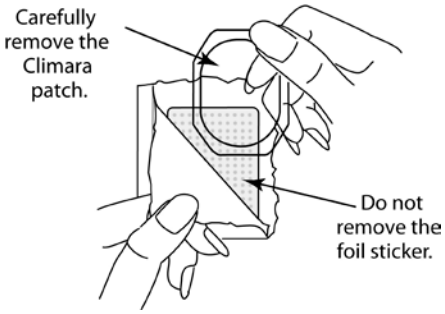


Figure E

Step 4. Placing the patch on your skin.

- Apply the sticky side of the patch to 1 of the areas of skin shown below. See **Figure F** and **Figure G**
- **Avoid** touching the sticky side of the patch with your fingers.

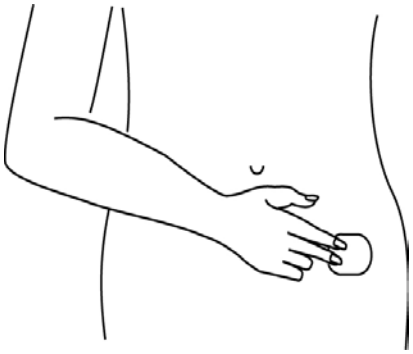


Figure F

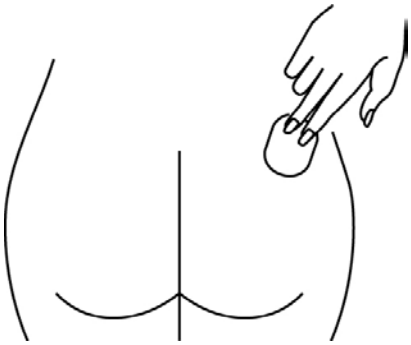


Figure G

Note:

- Avoid the waistline, since clothing and belts may cause the patch to be rubbed off.
- Do not apply Climara to your breasts.
- Only apply Climara to skin that is clean, dry, and free of any powder, oil, or lotion.
- You should not apply the patch 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 patch firmly onto your skin.

- Press the patch firmly in place with your fingers for at least 10 seconds
- Rub the edges of the patch to make sure that it will stick to your skin. (**See Figure H**)

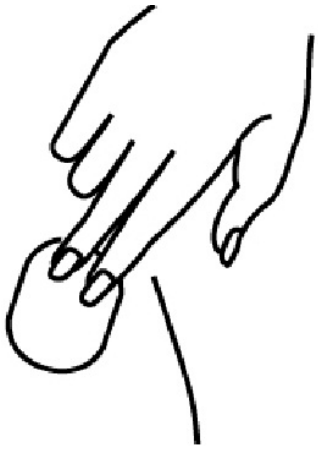


Figure H

Note:

- Contact with water while you are swimming, using a sauna, bathing, or showering may cause the patch to fall off.
- If your patch falls off reapply it. If you cannot reapply the patch, apply a new patch to another area (See Figures F and G), and continue to follow your original application schedule.
- If you stop using your Climara patch or forget to apply a new patch as scheduled, you may have spotting, or bleeding, and your symptoms may come back.

Step 6: Throwing away your used patch.

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

© 2013, Bayer HealthCare Pharmaceuticals Inc. All rights reserved.

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured by
3M Drug Delivery Systems

Northridge, CA 91324