

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

**WARNING: CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA, BREAST CANCER, and ENDOMETRIAL CANCER**

See full prescribing information for complete boxed warning.

### Estrogen Plus Progestin Therapy

- The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI) (5.1)
- The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)
- The WHI Memory Study (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)
- Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia (5.1, 5.3)

### Estrogen-Alone Therapy

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)
- The WHI estrogen-alone substudy reported increased risks of stroke and DVT (5.1)
- The 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)
- Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia (5.1, 5.3)

## RECENT MAJOR CHANGES

Boxed Warning

11/2021

## INDICATIONS AND USAGE

Climara Pro is an estrogen plus progestin indicated in a woman with a uterus for:

- Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause (1.1)
- Prevention of Postmenopausal Osteoporosis (1.2)

### Limitations of Use:

When prescribing solely for the prevention of postmenopausal osteoporosis, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA, BREAST CANCER, and ENDOMETRIAL CANCER

#### 1 INDICATIONS AND USAGE

- 1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause
- 1.2 Prevention of Postmenopausal Osteoporosis

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause
- 2.2 Prevention of Postmenopausal Osteoporosis
- 2.3 Application of the Climara Pro Transdermal System
- 2.4 Removal of the Climara Pro 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 pProgestogen When a Woman Has Not Had a Hysterectomy
- 5.8 Elevated Blood Pressure
- 5.9 Exacerbation of Hypertriglyceridemia

#### DOSAGE AND ADMINISTRATION

- Apply Climara Pro 0.045 mg per day/0.015 mg per day once-weekly to the lower abdomen (2.3)

#### DOSAGE FORMS AND STRENGTHS

- Transdermal system: 0.045 mg/day estradiol and 0.015 mg/day levonorgestrel (3)

#### CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4, 5.2)
- Breast cancer or a history of breast cancer (4, 5.2)
- 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 or hypersensitivity to Climara Pro (4)
- Hepatic impairment or disease (4, 5.10)
- Protein C, protein S, or antithrombin deficiency, or other thrombophilic disorders (4)

#### 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

- The most common adverse reactions (≥5 percent) with Climara Pro are: application site reaction, vaginal bleeding, breast pain, upper respiratory infection, back pain, depression, pain, headache and flu syndrome. (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](http://www.fda.gov/medwatch)

#### DRUG INTERACTIONS

- Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration. (7)
- Hydroxylation of levonorgestrel may interact with inhibitors of CYP3A, CYP2E and CYP2C and decrease the therapeutic effects. (7)

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

Revised: 11/2021

- 5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice
- 5.11 Exacerbation of 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

#### 8. USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

#### 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 in Postmenopausal Women

14.2 Effects on the Endometrium in Postmenopausal Women

14.3 Effects on Uterine Bleeding or Spotting in Postmenopausal Women

14.4 Effects on Bone Mineral Density in Postmenopausal Women

14.5 Women's Health Initiative Studies

14.6 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: CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA, BREAST  
CANCER, and ENDOMETRIAL CANCER**

**Estrogen Plus Progestin Therapy**

**Cardiovascular Disorders and Probable Dementia**

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported an increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [see *Warnings and Precautions* ([5.1](#)), and *Clinical Studies* ([14.5](#))].

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age and 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* ([14.6](#))].

Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia [see *Warnings and Precautions* ([5.1](#), [5.3](#)), and *Clinical Studies* ([14.5](#), [14.6](#))].

**Breast Cancer**

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer [see *Warnings and Precautions* ([5.2](#)), and *Clinical Studies* ([14.5](#))].

Only daily oral 0.625 mg CE and MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestogen therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

**Estrogen-Alone Therapy**

**Endometrial Cancer**

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestogen to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated 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**

The WHI estrogen-alone substudy reported increased risks of stroke and DVT in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral CE (0.625 mg)-alone, relative to placebo [see **Warnings and Precautions (5.1)**, and **Clinical Studies (14.5)**].

The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age and 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 (14.6)**].

Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia [see **Warnings and Precautions (5.1, 5.3)**, and **Clinical Studies (14.5, 14.6)**].

Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

## 1 INDICATIONS AND USAGE

Climara Pro is indicated for:

### 1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

### 1.2 Prevention of Postmenopausal Osteoporosis

#### Limitation of Use

When prescribing solely for the prevention of postmenopausal osteoporosis, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.

## 2 DOSAGE AND ADMINISTRATION

Use estrogen-alone, or in combination with a progestogen, at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Reevaluate postmenopausal women periodically as clinically appropriate to determine if treatment is still necessary.

One Climara Pro transdermal system is available for use.

### 2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Start therapy with Climara Pro 0.045 mg per day/0.015 mg per day applied to the skin once weekly. Start therapy at the lowest effective dose and the shortest duration consistent with the treatment goals. Attempts to discontinue Climara Pro should be made at 3 to 6 month intervals.

### 2.2 Prevention of Postmenopausal Osteoporosis

Apply Climara Pro 0.045 mg per day/0.015 mg per to the skin once weekly.

## **2.3 Application of the Climara Pro Transdermal System**

### Initiation of Therapy

Women not currently using continuous estrogen-alone therapy or estrogen plus progestogen therapy may start therapy with Climara Pro at any time. However, women currently using continuous estrogen-alone therapy or estrogen plus progestogen therapy should complete the current cycle of therapy before initiating Climara Pro 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 Climara Pro therapy.

### Site Selection

- Place the adhesive side of Climara Pro on a smooth (fold free), clean, dry area of the skin on the lower abdomen or the upper quadrant of the buttock.
- Do not apply Climara Pro to or near the breasts.
- Select an area selected that is not oily (which can impair adherence of the system), damaged, or irritated.
- Avoid the waistline; tight clothing may rub Climara Pro off or modify drug delivery.
- Avoid application to areas where sitting would dislodge Climara Pro.
- Rotate the sites of application, with an interval of at least 1-week allowed between applications to the same site.

### Application

- Apply Climara Pro immediately after opening the pouch and removing the protective lining.
- Press Climara Pro 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 the same system to another area of the lower abdomen. If the system cannot be reapplied, a new 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 7-day dosing interval.
- Do not expose the applied transdermal system to the sun for prolonged periods of time.
- Swimming, bathing, or using a sauna while using Climara Pro has not been studied, and these activities may decrease the adhesion of the system and the delivery of the estrogen and progestin.

## **2.4 Removal of the Climara Pro Transdermal System**

- Remove Climara Pro carefully and slowly to avoid irritation of the skin.
- If any adhesive remain on the skin after removal of Climara Pro, allow the area to dry for 15 minutes and then gently rub the area with an oil-based cream or lotion should remove the adhesive residue.
- Used patches still contain some active hormones. Carefully fold each patch in half so that it sticks to itself before throwing it away.

## **3 DOSAGE FORMS AND STRENGTHS**

Climara Pro (estradiol/levonorgestrel transdermal system) 0.045 mg/day estradiol and 0.015 mg/day levonorgestrel – each 22 cm<sup>2</sup> system contains 4.4 mg of estradiol and 1.39 mg of levonorgestrel.

## **4 CONTRAINDICATIONS**

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

- Undiagnosed abnormal genital bleeding [*see Warnings and Precautions (5.2)*]
- Breast cancer or history of breast cancer [*see Warnings and Precautions (5.2)*]
- Estrogen-dependent neoplasia [*see Warnings and Precautions (5.2)*]

- Active DVT, PE or a history of these conditions [*see Warnings and Precautions (5.1)*]
- Active arterial thromboembolic disease (for example, stroke or MI), or a history of these conditions [*see Warnings and Precautions (5.1)*]
- Known anaphylactic reaction, or angioedema, or hypersensitivity to Climara Pro
- Hepatic impairment or disease
- Protein C, protein S, or antithrombin deficiency, or other thrombophilic disorders

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Cardiovascular Disorders**

Increased risks of PE, DVT, stroke and MI are reported with estrogen plus progestin therapy. Increased risks of stroke and DVT are reported with estrogen-alone therapy. Immediately discontinue estrogen with or without progestogen therapy if any of these occur or are suspected.

Manage appropriately any 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).

#### Stroke

The WHI estrogen plus progestin substudy reported a statistically significant increased risk of stroke 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 strokes per 10,000 women-years, respectively) [*see Clinical Studies (14.5)*]. The increase in risk was demonstrated after the first year and persisted.<sup>1</sup> Immediately discontinue estrogen plus progestogen therapy if a stroke occurs or is suspected.

The WHI estrogen-alone substudy, reported a statistically significant increased risk of stroke 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 strokes per 10,000 women-years, respectively). The increase in risk was demonstrated in year 1 and persisted [*see Clinical Studies (14.5)*]. Immediately discontinue estrogen-alone therapy if a stroke occurs or is suspected.

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).<sup>1</sup>

#### Coronary Heart Disease

The WHI estrogen plus progestin substudy reported an increased risk (not statistically significant) of coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) 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).<sup>1</sup> 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 (14.5)*].

The WHI estrogen-alone substudy reported no overall effect on CHD events in women receiving estrogen-alone compared to placebo<sup>2</sup> [*see Clinical Studies (14.5)*].

Subgroup analyses of women 50 to 59 years of age, who were less than 10 years since menopause, suggest a reduction (not statistically significant) of CHD events in those women receiving CE (0.625 mg)-alone compared to placebo (8 versus 16 per 10,000 women-years).<sup>1</sup>

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established CHD. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

## Venous Thromboembolism

The WHI estrogen plus progestin substudy reported a statistically significant 2-fold greater rate of VTE (DVT and PE) 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<sup>3</sup> [see *Clinical Studies* (14.5)]. Immediately discontinue estrogen plus progestogen therapy if a VTE occurs or is suspected.

In the WHI estrogen-alone substudy, the risk of VTE 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<sup>4</sup> [see *Clinical Studies* (14.5)]. Immediately discontinue estrogen-alone therapy if a VTE occurs or is suspected.

If feasible, discontinue estrogens 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**

### Breast Cancer

After a mean follow-up of 5.6 years, the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg) reported an increased risk of invasive breast cancer in women who took daily CE plus MPA compared to placebo.

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. 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<sup>5</sup> [see *Clinical Studies* (14.5)].

The WHI substudy of daily CE (0.625 mg)-alone provided information about breast cancer in estrogen-alone users. 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*]<sup>6</sup> [see *Clinical Studies* (14.5)].

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer with estrogen plus progestin therapy, and a smaller increase in the risk for breast cancer with 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. 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.

### 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 nonusers, 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 progestogen therapy is important. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding with unknown etiology.

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

### Ovarian Cancer

The CE plus MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24), but it was not statistically significant. The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.<sup>7</sup>

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.

### **5.3 Probable Dementia**

In the WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI, 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<sup>8</sup> [see *Use in Specific Populations (8.5)*, and *Clinical Studies (14.6)*].

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<sup>8</sup> [see *Use in Specific Populations (8.5)*, and *Clinical Studies (14.6)*].

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<sup>8</sup> [see *Use in Specific Populations (8.5)*, and *Clinical Studies (14.6)*].

### **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. Discontinue estrogens, including Climara Pro if hypercalcemia occurs, and take appropriate measures to reduce the serum calcium level.

### **5.6 Visual Abnormalities**

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue Climara Pro pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Permanently discontinue estrogens, including Climara Pro, if examination reveals papilledema or retinal vascular lesions.

### **5.7 Addition of a Progestogen When a Woman Has Not Had a Hysterectomy**

Studies of the addition of a progestogen 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 progestogens 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 Exacerbation of Hypertriglyceridemia**

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Discontinue Climara Pro if pancreatitis occurs.

### **5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice**

Estrogens may be poorly metabolized in women with hepatic impairment. Exercise caution in any woman with a history of cholestatic jaundice associated with past estrogen use or with pregnancy. In the case of recurrence of cholestatic jaundice, discontinue Climara Pro.

### **5.11 Exacerbation of 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<sub>4</sub> and T<sub>3</sub> 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. Monitor thyroid function in these women during treatment with Climara Pro to maintain their free thyroid hormone levels in an acceptable range.

### **5.12 Fluid Retention**

Estrogens plus progestogens may cause some degree of fluid retention. Monitor any woman with a condition(s) that might predispose her to fluid retention, such as a cardiac or renal impairment. Discontinue estrogens plus progestogens therapy, including Climara Pro, with evidence of medically concerning fluid retention.

### **5.13 Hypocalcemia**

Estrogen-induced hypocalcemia may occur in women with hypoparathyroidism. Consider whether the benefits of estrogen therapy, including Climara Pro, outweigh the risks in such women.

### **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.

### **5.15 Hereditary Angioedema**

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. Consider whether the benefits of estrogen therapy, including Climara Pro, outweigh the risks in such women.

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

Estrogen therapy, including Climara Pro, may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas. Consider whether the benefits of estrogen therapy outweigh the risks 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 postmenopausal women with moderate to severe vasomotor symptoms.

### 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<sub>4</sub> levels (by column or by radioimmunoassay) or T<sub>3</sub> levels by radioimmunoassay. T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG. Free T<sub>4</sub> and free T<sub>3</sub> concentrations are unaltered. 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-1-antitrypsin, ceruloplasmin).
- Increased plasma high-density lipoprotein (HDL) and HDL<sub>2</sub> cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, and in oral formulations increased triglycerides levels.
- Impaired glucose tolerance.

## 6 ADVERSE REACTIONS

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

- Cardiovascular Disorders [see *Boxed Warning, Warnings and Precautions (5.1)*]
- Malignant Neoplasms [see *Boxed Warning, 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 is from a one-year, prospective, multicenter, double blind, double dummy, randomized, controlled trial investigating the effect of three different dosage combinations of E<sub>2</sub>/LNG versus E<sub>2</sub> alone on the development of endometrial hyperplasia. All women were postmenopausal, had a serum estradiol level of less than 20 pg/mL, and the sample included both symptomatic and asymptomatic women. The data below includes all adverse reactions reported at a frequency of >3% in the E<sub>2</sub>/LNG 0.045 / 0.015 group (the approved dosage for Climara Pro, N=212) and the E<sub>2</sub> alone group (N=204).

**Table 1: All Treatment Emergent Reactions Regardless of Relationship Reported at a Frequency of >3% with Climara Pro in the 1-year Endometrial Hyperplasia Study**

Body System Adverse Reaction	Climara Pro 0.045 / 0.015	E <sub>2</sub>
	N <sup>a</sup> = 212	N = 204
<b>Body as a Whole</b>		
Abdominal pain	9 (4.2)	11 (5.4)
Accidental injury	7 (3.3)	6 (2.9)
Back pain	13 (6.1)	12 (5.9)
Flu syndrome	10 (4.7)	13 (6.4)
Infection	7 (3.3)	10 (4.9)
Pain	11 (5.2)	13 (6.4)
<b>Cardiovascular System</b>		
Hypertension	7 (3.3)	9 (4.4)
<b>Digestive System</b>		
Flatulence	8 (3.8)	11 (5.4)
<b>Metabolic and Nutritional</b>		

Edema	8 (3.8)	5 (2.5)
Weight gain	6 (2.8)	10 (4.9)
<b>Musculoskeletal System</b>		
Arthralgia	9 (4.2)	10 (4.9)
<b>Nervous System</b>		
Depression	12 (5.7)	7 (3.4)
Headache	11 (5.2)	14 (6.9)
<b>Respiratory System</b>		
Bronchitis	9 (4.2)	7 (3.4)
Sinusitis	8 (3.8)	12 (5.9)
Upper respiratory infection	28 (13.2)	26 (12.7)
<b>Skin and Appendages</b>		
Application site reaction	86 (40.6)	69 (33.8)
Breast pain	40 (18.9)	20 (9.8)
Rash	5 (2.4)	10 (4.9)
<b>Urogenital System</b>		
Urinary Tract Infection	7 (3.3)	8 (3.9)
Vaginal Bleeding	78 (36.8)	44 (21.6)
Vaginitis	4 (1.9)	6 (2.9)

a) N = total number of subjects in a treatment group; n = number of subjects with event.

Irritation potential of Climara Pro was assessed in a 3-week irritation study. The study compared the irritation of a Climara Pro placebo patch (22 cm<sup>2</sup>) to a placebo (25 cm<sup>2</sup>). Visual assessments of irritation were made on Day 7 of each wear period, approximately 30 minutes after patch removal using a 7-point scale (0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible, or minimal edema, or minimal papular response; 3–7 = erythema and papules, edema, vesicles, strong extensive reaction).

The mean irritation scores were 0.13 (week 1), 0.12 (week 2), and 0.06 (week 3) for the Climara Pro. The mean scores for the placebo group were 0.2 (week 1), 0.26 (week 2), 0.12 (week 3). There were no irritation scores greater than 2 at any timepoint in any woman.

In controlled clinical trials, withdrawals due to application site reactions occurred in 6 (2.1 percent) of women in the 12-week symptom study and in 71 (8.5 percent) of subjects in the 1-year endometrial protection study.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Climara Pro. 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.

### Genitourinary System

Changes in bleeding patterns

### Gastrointestinal

Abdominal distension,\* abdominal pain,\* nausea

### Skin

Alopecia, night sweats, pruritus,\* Rash,\* hot flush\*

### Central Nervous System

Dizziness, headache, insomnia

### Miscellaneous

Application site reaction,\* weight increased, anaphylactic reaction

\* Combined two or more similar ARs

## 7 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 (*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 adverse reactions.

Hydroxylation of levonorgestrel is a conversion step, which is mediated by cytochrome P450 enzymes. Based on *in-vitro* and *in vivo* studies, it can be assumed that CYP3A, CYP2E and CYP2C are involved in the metabolism of levonorgestrel. Likewise, inducers or inhibitors of these enzymes may either, respectively, decrease the therapeutic effects or result in adverse reactions.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Climara Pro is not indicated for use in pregnancy. There are no data with the use of Climara Pro in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives (estrogens and progestins) before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

### 8.2 Lactation

#### Risk Summary

Estrogens plus progestogens are present in human milk and can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Climara Pro and any potential adverse effects on the breastfed child from Climara Pro or from the underlying maternal condition.

### 8.4 Pediatric Use

Climara Pro is not indicated for use in pediatric patients. 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 Pro to determine whether those over 65 years of age differ from younger subjects in their response to Climara Pro.

#### *The Women's Health Initiative Studies*

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age [*see Clinical Studies (14.5)*].

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 (14.5)*].

#### *The Women's Health Initiative Memory Study*

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen plus progestin or estrogen-alone when compared to placebo [*see Warnings and Precautions (5.3), and Clinical Studies (14.6)*].

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<sup>8</sup> (*see Warnings and Precautions (5.3), and Clinical Studies (14.6)*).

## 10 OVERDOSAGE

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

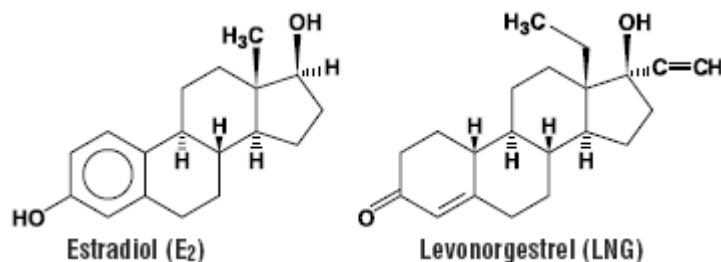
## 11 DESCRIPTION

Climara Pro (estradiol/levonorgestrel transdermal system) is an adhesive-based matrix transdermal patch designed to release both estradiol and levonorgestrel, a progestational agent, continuously upon application to intact skin. The 22 cm<sup>2</sup> Climara Pro system contains 4.4 mg estradiol and 1.39 mg levonorgestrel and provides a nominal delivery rate (mg per day) of 0.045 estradiol and 0.015 levonorgestrel.

Estradiol USP has a molecular weight of 272.39 and the molecular formula is C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>.

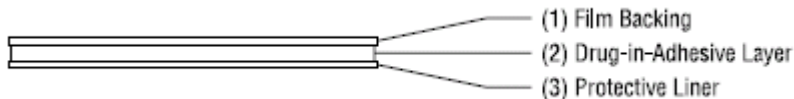
Levonorgestrel USP has a molecular weight of 312.4 and a molecular formula of C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>.

The structural formulas for estradiol and levonorgestrel are:



The Climara Pro transdermal system comprises 3 layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are:

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



The active components of the transdermal system are estradiol and levonorgestrel. The remaining components of the transdermal system (acrylate copolymer adhesive and polyvinylpyrrolidone/vinyl acetate copolymer) 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.

Levonorgestrel inhibits gonadotropin production resulting in retardation of follicular growth and inhibition of ovulation.

Studies to assess the potency of progestins using estrogen-primed postmenopausal endometrial biochemistry and morphologic features have shown that levonorgestrel counteracts the proliferative effects of estrogens on the endometrium.

## 12.2 Pharmacodynamics

Generally, a serum estrogen concentration does not predict an individual woman's therapeutic response to Climara nor her risk for adverse outcomes. Likewise, exposure comparisons across different estrogen products to infer efficacy or safety for the individual woman may not be valid.

## 12.3 Pharmacokinetics

### Absorption

Transdermal administration of Climara Pro produces mean maximum estradiol concentrations in serum in about 2 to 2.5 days. Estradiol concentrations equivalent to the normal ranges observed at the early follicular phase in premenopausal women are achieved within 12–24 hours after the first application.

In one study, steady state estradiol concentrations in serum were measured during week 4 in 44 healthy, postmenopausal women during four consecutive Climara Pro applications of two formulations (0.045 mg estradiol/0.03 mg levonorgestrel and 0.045 mg estradiol/0.015 mg levonorgestrel) to the abdomen (each dose was applied for four 7-day periods). Both formulations were bioequivalent in terms of estradiol and estrone  $C_{max}$  and AUC parameters. A summary of Climara Pro single and multiple applications estradiol, estrone and levonorgestrel pharmacokinetic parameters is shown in Table 2.

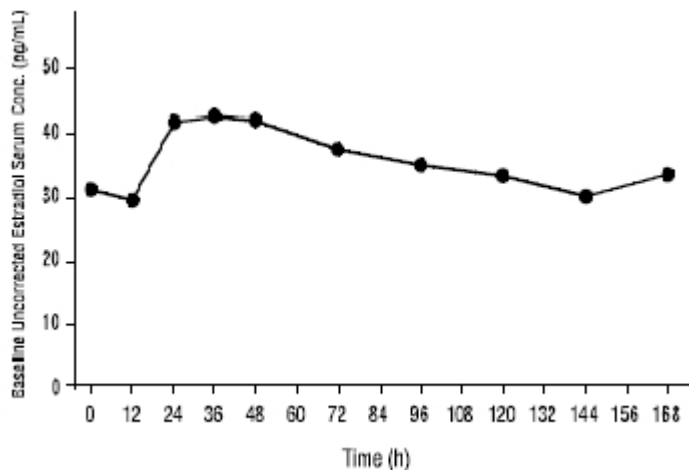
**Table 2: Summary of Mean Pharmacokinetic Parameters**

<b>Summary of Mean (<math>\pm</math> SD) Pharmacokinetic Parameters Following a Single Application of Climara Pro in 24 Healthy Postmenopausal Women</b>				
<b>Parameter</b>	<b>Units</b>	<b>Estradiol</b>	<b>Estrone</b>	<b>Levonorgestrel</b>
Single application Week 1 Data				
$C_{ave}$	Pg/mL	37.7 $\pm$ 10.4	41 $\pm$ 15	136 $\pm$ 52.7
$C_{max}$	Pg/mL	54.3 $\pm$ 18.9	43.9 $\pm$ 14.9	138 $\pm$ 51.8
$T_{max}$	Hours	42	84	90
$C_{min}$	Pg/mL	27.2 $\pm$ 7.66	32.6 $\pm$ 14.3	110 $\pm$ 41.7
AUC	Pg.h/mL	6340 $\pm$ 1740	6890 $\pm$ 2520	22900 $\pm$ 8860
<b>Summary of Mean (<math>\pm</math> SD) Pharmacokinetic Parameters (Week 4) Following Four Consecutive Weekly Applications of Climara Pro in 44 Healthy Postmenopausal Women</b>				
Multiple application Week 4 Data				
$C_{ave}$	Pg/mL	35.7 $\pm$ 11.4	45.5 $\pm$ 62.6	166 $\pm$ 97.8
$C_{max}$	Pg/mL	50.7 $\pm$ 28.6	81.6 $\pm$ 252	194 $\pm$ 111
$T_{max}$	Hours	36	48	48
$C_{min}$	Pg/mL	33.8 $\pm$ 28.7	72.5 $\pm$ 253	153 $\pm$ 69.6
AUC	Pg.h/mL	6002 $\pm$ 1919	7642 $\pm$ 10518	27948 $\pm$ 16426

All mean parameters are arithmetic means except  $T_{max}$  which is expressed as the median.

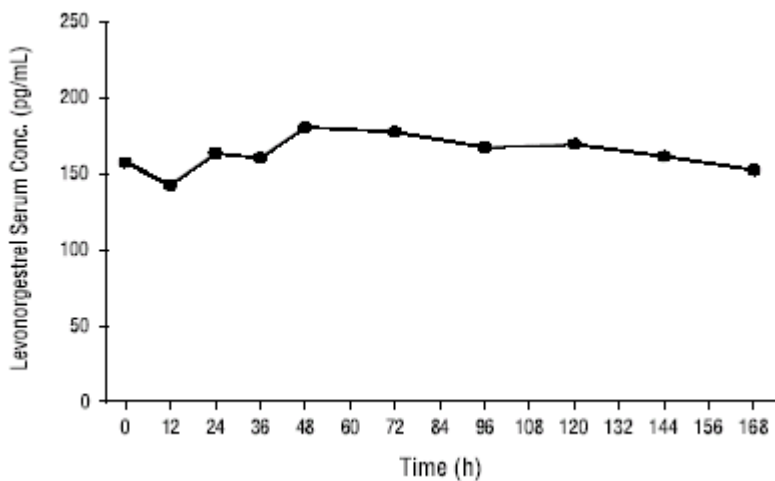
At steady state, Climara Pro maintains during the application period an average serum estradiol concentration of 35.7 pg/mL as depicted in Figure 1.

**Figure 1: Mean Estradiol Concentration Profile (Week 4)  
Following Four Consecutive Weekly Applications of Climara Pro**



Following the application of the Climara Pro transdermal system, levonorgestrel concentrations are maximum in about 2.5 days. At steady state, Climara Pro maintains during the application period an average serum levonorgestrel concentration of 166 pg/mL as depicted in Figure 2. The mean levonorgestrel pharmacokinetic parameters of Climara Pro are summarized in Table 2.

**Figure 2: Mean Levonorgestrel Concentration Profile (Week 4)  
Following Four Consecutive Weekly Applications of Climara Pro**



### 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.

Levonorgestrel in serum is bound to both SHBG and albumin. Following four consecutive weekly applications of Climara Pro mean ( $\pm$  SD) SHBG concentrations declined from a predose value of 47.5 (25.8) to 41.2 (22.4) nmol/L at week 4.

### 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.

The most important metabolic pathway for levonorgestrel occurs in the reduction of the  $\Delta^4$ - and the 3-oxo-group as well as hydroxylations at positions 2 $\alpha$ , 1 $\beta$ , and 16 $\beta$ , followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3 $\alpha$ , 5 $\beta$ -tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as the 17 $\beta$ -sulfate. *In-vitro* studies on the biotransformation of levonorgestrel in human skin did not indicate any significant metabolism of levonorgestrel during skin penetration.

### Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Following patch removal, serum estradiol concentrations decline with a mean ( $\pm$  SD) terminal half-life of  $3 \pm 0.67$  hours.

Levonorgestrel and its metabolites are primarily excreted in the urine. Mean ( $\pm$  SD) terminal half-life for levonorgestrel was determined to be  $28 \pm 6.4$  hours.

### Adhesion

A study of the adhesion potential of Climara Pro was conducted in 104 healthy women of 45–75 years of age. Each woman applied a placebo patch, containing only the Climara Pro adhesive without active ingredient, to the upper outer abdominal areas weekly for three weeks. The adhesion assessment was done visually on Days 2, 4, 5, 6 and 7 of each of the three weeks using a four-point scale. The mean scores ranked in the highest category possible on the 0 to 4 scale demonstrating clinically acceptable adhesion performance.

## 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 in Postmenopausal Women

The efficacy of 0.045 mg estradiol/0.03 mg levonorgestrel administered weekly versus placebo in the relief of moderate to severe vasomotor symptoms in postmenopausal women was studied in one 12-week clinical trial (n=183, average age  $52.1 \pm 4.93$ , 82 percent Caucasian). The 0.045 mg estradiol/0.03 mg levonorgestrel dosage strength was shown to be statistically better than placebo at weeks 4 and 12 for relief of both the number and severity of moderate to severe hot flushes. See Tables 3 and 4. Climara Pro and the 0.045 mg estradiol/0.03 mg levonorgestrel dosage strength are bioequivalent in terms of estradiol delivery [See *Clinical Pharmacology* ([12.3](#))].

**Table 3: Summary of Mean Daily Number of Moderate to Severe Hot Flushes-ITT<sup>a</sup>**

		Baseline <sup>b</sup>	Week 4	Week 8	Week 12
Placebo	n <sup>c</sup>	88	82	73	69
	Mean (SD) <sup>d</sup>	10.8 (5.803)	6.13 (4.311)	5.35 (4.095)	5.59 (4.93)
	Mean Change from baseline (SD)	NA	-4.23 (4.374)	-4.8 (4.448)	-4.55 (5.407)
0.045/.03	n <sup>c</sup>	92	88	80	73
	Mean (SD) <sup>d</sup>	10.13 (3.945)	2.69 (4.455)	1.22 (2.804)	1.06 (3.187)
	Mean Change from baseline (SD) <sup>d</sup>	NA	-7.4 (4.715)	-8.68 (4.146)	-8.82 (4.336)

p-Value <sup>e</sup>		NA	<0.001 <sup>f</sup>	NA	<0.001 <sup>f</sup>
----------------------	--	----	---------------------	----	---------------------

- a) ITT = Intent-to-Treat population
- b) A participating woman was included at baseline only if she had a post-baseline mean score. The post-baseline mean score required 3 days in one week.
- c) n = Number of participating women in a treatment group in a cycle; number of women varied from cycle to cycle due to missing data
- d) SD = standard deviation
- e) p-value for comparison to placebo, adjusted by the method of Bonferroni
- f) p < 0.025

**Table 4: Summary of Mean Severity of Moderate to Severe Hot Flashes-ITT<sup>a</sup>**

		Baseline <sup>b</sup>	Week 4 (day 7)	Week 8 (day 7)	Week 12 (day 7)
Placebo	n <sup>c</sup>	89	76	68	57
	Mean (SD) <sup>d</sup>	2.42 (0.282)	1.99 (0.875)	1.93 (0.955)	1.8 (1.034)
	Mean Change from baseline (SD) <sup>d</sup>	NA	-0.4 (0.865)	-0.48 (0.922)	-0.57 (1.044)
0.045/.03	n <sup>c</sup>	92	83	72	55
	Mean (SD) <sup>d</sup>	2.48 (0.295)	1.1 (1.191)	0.82 (1.226)	0.44 (0.96)
	Mean Change from baseline (SD) <sup>d</sup>	NA	-1.4 (1.164)	-1.67 (1.245)	-2.06 (1.005)
p-value <sup>e</sup>		NA	<0.001 <sup>f</sup>	NA	<0.001 <sup>f</sup>

- a) ITT= Intent-to-Treat population
- b) A participating woman was included at baseline only if she had at least 1 post-baseline value.
- c) n= Number of participating women in a treatment group in a cycle; number of women varied from cycle to cycle due to missing data
- d) SD= standard deviation Severity scores are: 1 = Mild, 2 = Moderate, 3 = Severe. Mean severity of hot flashes by day is [(2X number of moderate hot flashes) + (3X number of severe hot flashes)] / total number of moderate to severe hot flashes on that day. If no moderate to severe hot flush was indicated, the mean severity was 0.
- e) p-value for comparison to placebo, adjusted by the method of Bonferroni
- f) p < 0.025

#### 14.2 Effects on the Endometrium in Postmenopausal Women

In a 1-year clinical trial of 412 postmenopausal women (with intact uteri) treated with a continuous regimen of Climara Pro or with an continuous estradiol-only transdermal system, results of evaluable endometrial biopsies show that no hyperplasia was seen with Climara Pro. Table 5 below summarizes these results (Intent-to-Treat populations).

**Table 5: Incidence of Endometrial Hyperplasia during Continuous Combined Treatment with Climara Pro, ITT<sup>f</sup>**

	Climara Pro E <sub>2</sub> 0.045 mg / LNG 0.015 mg	Estradiol E <sub>2</sub> 0.045 mg
	n <sup>a</sup> = 210	n <sup>a</sup> = 202
No. of Patients with Biopsies at >6 months <sup>b</sup>	124	139
No. of Patients with Biopsies at 1 year <sup>c</sup>	102	110
No. (%) of Patients with Hyperplasia <sup>d</sup>	0 (0%) <sup>e</sup>	19 (17.3%)
95% Confidence Interval	0-3.55%	9.75–24.79%

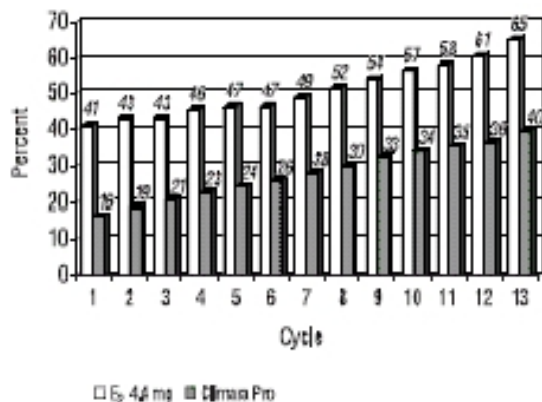
- a) n = number of intent-to-treat participating women.

- b) Defined as at least 180 days of treatment.
- c) Defined as  $\geq 323$  days of treatment.
- d) Includes hyperplasia occurring at any time after initiation of treatment as a proportion of patients with biopsies at 1 year.
- e)  $p < 0.0167$  p-value for comparison to unopposed estradiol dose using the Fisher Exact test. P-values were adjusted by the method of Bonferroni.
- f) ITT = Intent-to-Treat population.

### 14.3 Effects on Uterine Bleeding or Spotting in Postmenopausal Women

The effects of Climara Pro on uterine bleeding or spotting, as recorded using an interactive voice response system, were evaluated in one 12-month clinical trial. Results are shown in Figure 3.

**Figure 3: Cumulative Proportion of Subjects at Each Cycle with No Bleeding/Spotting Through the End of Cycle 13 Last Observation Carried Forward**



- Percent based upon the number of participating women with data
- Last non-missing cycle carried forward through cycle 13
- Bleeding associated with endometrial biopsies not included

### 14.4 Effects on Bone Mineral Density in Postmenopausal Women

The effects on bone mineral density (BMD) were studied in a randomized, double-blind, placebo-controlled clinical trial of transdermal systems (patches) containing only estradiol (E<sub>2</sub>). Participants were postmenopausal women with hysterectomies, 40–83 years of age (mean=51.4 years), and 77.3 percent Caucasian. Women received calcium supplements if they appeared deficient on a questionnaire. Vitamin D supplements were not given.

A total of 154 women were randomized in a 2:2:3 ratio to weekly application of 22 cm<sup>2</sup> patches containing 2.2 mg E<sub>2</sub>, 4.4 mg E<sub>2</sub>, or placebo, for 728 days of continuous treatment (26 28-day cycles). Only the results for the estradiol dose in Climara Pro (4.4 mg E<sub>2</sub>) and for placebo are presented.

Statistically significant increases in the primary efficacy variable, BMD of the lumbar spine (A-P view, L2-L4), were seen for 4.4 mg E<sub>2</sub> compared to placebo (see Table 5 and Figure 4). BMD was also measured at the hip (total, non-dominant side) and radius (midshaft, non-dominant side) with statistically significant treatment effects only observed for the hip (see Table 6).

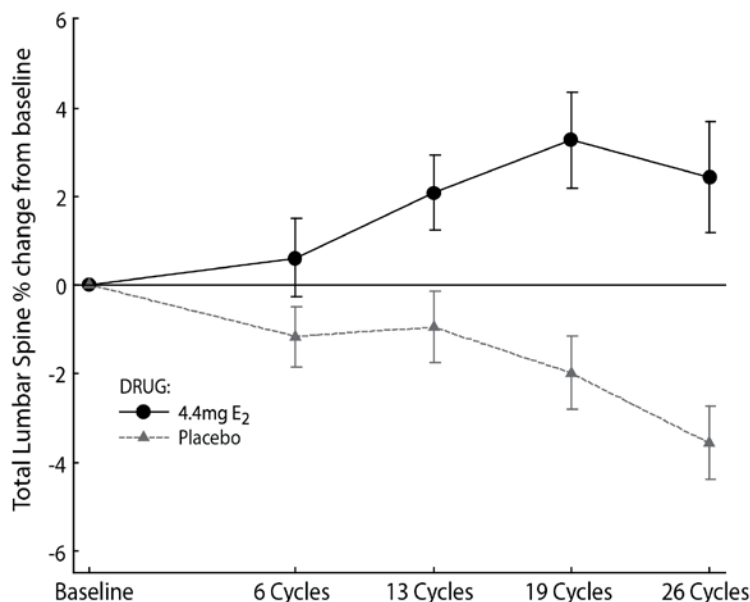
**Table 6: Mean Bone Mineral Density (Standard Deviation)<sup>a</sup>**

	<b>4.4 mg E<sub>2</sub><sup>b</sup></b>	<b>Placebo</b>
Total Lumbar Spine	n=36	n=46
Baseline (g/cm <sup>2</sup> )	1.1 (0.2)	1.1 (0.2)
% Change from baseline LOCF	+1.7% (4.4)	-2.9% (3.8)
P-value compared to placebo	<0.0001	
Total Hip	n=36	n=48
Baseline (g/cm <sup>2</sup> )	0.97 (0.1)	0.94 (0.1)
% Change from baseline LOCF	+1.3% (4.2)	-0.9% (5.2)
P-value compared to placebo	0.05	

a) Intent-to-treat population with on-treatment efficacy data

b) E<sub>2</sub>=estradiol; LOCF= Last Observation Carried Forward

**Figure 4: Percent Change From Baseline in Bone Mineral Density (g/cm<sup>2</sup>) of Lumbar Spine (A-P View, L2–L4) by Treatment Group and Cycle (Mean ± SE)\***



\* Data in the figure is for 21 patients on 4.4 mg E<sub>2</sub> and 27 placebo patients who completed the study; approximately 44 percent of randomized patients.

### 14.5 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 cause. These substudies did not evaluate the effects of CE plus MPA or CE-alone on menopausal symptoms.

#### WHI Estrogen Plus Progestin Substudy

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

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8

more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

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

**Table 7: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years<sup>a, b</sup>**

Event	Relative Risk CE/MPA vs. Placebo (95% nCI <sup>c</sup> )	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
<i>Non-fatal MI</i>	1.28 (1.00-1.63)	31	25
<i>CHD death</i>	1.10 (0.70-1.75)	8	8
All strokes	1.31 (1.03-1.68)	33	25
<i>Ischemic stroke</i>	1.44 (1.09-1.90)	26	18
Deep vein thrombosis <sup>d</sup>	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer <sup>e</sup>	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer <sup>d</sup>	0.81 (0.48-1.36)	6	7
Cervical cancer <sup>d</sup>	1.44 (0.47-4.42)	2	1
Hip fracture <sup>c</sup>	0.67 (0.47-0.96)	11	16
Vertebral fractures <sup>d</sup>	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures <sup>d</sup>	0.71 (0.59-0.85)	44	62
Total fractures <sup>d</sup>	0.76 (0.69-0.83)	152	199
Overall Mortality <sup>f</sup>	1.00 (0.83-1.19)	52	52
Global Index <sup>g</sup>	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](http://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, colorectal cancer, hip fracture, or death due to other causes.

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

#### *WHI Estrogen-Alone Substudy*

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

Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, 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 8.

**Table 8. Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI<sup>a</sup>**

Event	Relative Risk CE vs. Placebo (95% nCI <sup>b</sup> )	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events <sup>c</sup>	0.95 (0.78-1.16)	54	57
<i>Non-fatal MI<sup>c</sup></i>	<i>0.91 (0.73-1.14)</i>	<i>40</i>	<i>43</i>
<i>CHD death<sup>c</sup></i>	<i>1.01 (0.71-1.43)</i>	<i>16</i>	<i>16</i>
All strokes <sup>c</sup>	1.33 (1.05-1.68)	45	33
<i>Ischemic stroke<sup>c</sup></i>	<i>1.55 (1.19-2.01)</i>	<i>38</i>	<i>25</i>
Deep vein thrombosis <sup>c, d</sup>	1.47 (1.06-2.06)	23	15
Pulmonary embolism <sup>c</sup>	1.37 (0.90-2.07)	14	10
Invasive breast cancer <sup>c</sup>	0.80 (0.62-1.04)	28	34
Colorectal cancer <sup>c</sup>	1.08 (0.75-1.55)	17	16
Hip fracture <sup>c</sup>	0.65 (0.45-0.94)	12	19
Vertebral fractures <sup>c, d</sup>	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures <sup>c, d</sup>	0.58 (0.47-0.72)	35	59
Total fractures <sup>c, d</sup>	0.71 (0.64-0.80)	144	197
Death due to other causes <sup>e, f</sup>	1.08 (0.88-1.32)	53	50
Overall Mortality <sup>c, d</sup>	1.04 (0.88-1.22)	79	75
Global Index <sup>g</sup>	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](http://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/probable CHD, PE or cerebrovascular disease.
- g) A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE- alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.<sup>9</sup> 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.

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

Timing of the 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 [*HR 0.63 (95 percent CI, 0.36-1.09)*] and overall mortality [*HR 0.71 (95 percent CI, 0.46-1.11)*].

#### 14.6 Women's Health Initiative Memory Study

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 to 79 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 was 45 versus 22 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see *Warnings and Precautions* (5.3), and *Use in Specific Populations* (8.5)].

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 years of age and older (45 percent were age 65 to 69 years of age, 36 percent were 70 to 74 years of age, and 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 this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo groups 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 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. Cushman M, et al. Estrogen Plus Progestin and Risk of Venous Thrombosis. *JAMA*. 2004;292:1573-1580.
4. Curb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus. *Arch Int Med*. 2006;166:772-780.
5. Chlebowski RT, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. *JAMA*. 2003;289:3234-3253.
6. 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.
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

#### Individual Carton of 4 systems

Climara Pro (estradiol/levonorgestrel transdermal system) 0.045 mg/day estradiol and 0.015 mg/day levonorgestrel – each 22 cm<sup>2</sup> system contains 4.4 mg of estradiol and 1.39 mg of levonorgestrel. NDC 50419-491-04

### 16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP controlled Room Temperature].

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

Used transdermal systems still contain active hormones. 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

Advise women to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

### **Vaginal Bleeding**

Inform postmenopausal women to report any vaginal bleeding to their healthcare provider as soon as possible [*see Warning and Precautions (5.2)*].

### **Possible Serious Adverse Reactions with Estrogen Plus Progestogen Therapy**

Inform postmenopausal women of possible serious adverse reactions of estrogen plus progestogen therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia [*see Warning and Precautions (5.1, 5.2, 5.3)*].

### **Possible Common Adverse Reactions with Estrogen plus Progestogen Therapy**

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

## Patient Information

### Climara Pro (Klī-mār-uh prō)

(estradiol/levonorgestrel transdermal system)

Read this Patient Information before you start using Climara Pro 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 Pro (a combination of estrogen and progestogen)?**

- Do not use estrogens with or without progestogens to prevent heart disease, heart attacks, strokes, or dementia (declines of brain function).
- Using estrogens with progestogens may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestogens may increase your chance of getting dementia, based on a study of women 65 years of age and older.
- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb).
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia.
- 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 65 years of age and older.
- Only one estrogen with progestogen product and dose have been shown to increase your chances of getting heart attacks, strokes, breast cancer, blood clots, and dementia. Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, blood clots, and dementia.

Because other products and doses have not been studied in the same way, it is not known how the use of Climara Pro will affect your chances of these conditions. You and your healthcare provider should talk regularly about whether you still need treatment with Climara Pro.

#### **What is Climara Pro?**

Climara Pro is a prescription medicine patch (transdermal system) that contains two kinds of hormones, an estrogen and a progestogen.

#### **What is Climara Pro used for?**

Climara Pro 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 intense 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.

- **Help reduce your chances of getting osteoporosis (thin weak bones)**

Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use Climara Pro to prevent osteoporosis from 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 Pro.

### **Who should not use Climara Pro?**

#### **Do not use Climara Pro if you have had your uterus (womb) removed (hysterectomy).**

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

#### **Do not start using Climara Pro 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 been diagnosed with a bleeding disorder**

- **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 (womb). If you have or have had cancer, talk with your healthcare provider about whether you should use Climara Pro.

- **had a stroke or heart attack**

- **currently have or have had blood clots**

- **currently have or have had liver problems**

- **are allergic to Climara Pro or any of the ingredients in it.**

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

#### **Before you use Climara Pro, tell your healthcare provider about all of your medical conditions, including 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 that may become worse while you are using Climara**

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 Pro.

- **are pregnant or think you may be pregnant.**

Climara is not for pregnant women.

- **are breastfeeding**

The hormones in Climara Pro can pass into your breast milk.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may affect how Climara Pro works. Climara Pro 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 a new medicine.

### **How should I use Climara Pro?**

**For detailed instructions, see the step-by-step instructions for using Climara Pro at the end of this Patient Information.**

- Use Climara Pro exactly as your healthcare provider tells you to use it.
- Climara Pro is for skin use only.
- Change your Climara Pro patch 1 time each week or every 7 days.
- Apply your Climara Pro 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 Pro 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 Pro to your breasts.
- If you forget to apply a new Climara Pro, 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 Pro.

### **How do I change Climara Pro?**

- When changing Climara Pro, peel off the used patch slowly from the skin.
- After removal of Climara Pro, 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.
- Apply the new patch to a different skin area of your lower abdomen or buttocks. This area must be clean, dry, and free of powder, oil or lotion. Do not use the same site again for at least 1 week after removal of the patch.

### **What are the possible side effects of Climara Pro?**

**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
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- dementia
- high or low blood calcium
- gallbladder disease
- visual abnormalities

- high blood pressure
- cancer changes of endometriosis
- high levels of fat (triglyceride) in your blood
- liver problems
- changes in your thyroid hormone levels
- fluid retention
- enlargement of benign tumors of the uterus (“fibroids”)
- worsening of swelling of face and tongue (angioedema) in women with a history of angioedema

**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

**Common side effects of Climara Pro include:**

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

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

You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Bayer Healthcare Pharmaceuticals at 1-888-842-2937.

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

- Talk with your healthcare provider regularly about whether you should continue using Climara Pro.
- If you have a uterus, talk with your healthcare provider about whether Climara Pro is right for you. In general, the addition of a progestogen is generally recommended for a woman 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 Pro.
- 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 Pro?**

- Store at room temperature between 68°F to 77°F (20°C to 25°C).

- Do not store Climara Pro patches outside of their pouches. Apply immediately after 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 PRO and all medicines out of the reach of children.**

### General information about the safe and effective use of Climara Pro.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use Climara Pro for conditions for which it was not prescribed. Do not give Climara Pro to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about Climara Pro that is written for health professionals. For more information, go to [www.climara-us.com](http://www.climara-us.com) or call Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937.

### What are the ingredients in Climara Pro?

**Active ingredient:** estradiol and levonorgestrel

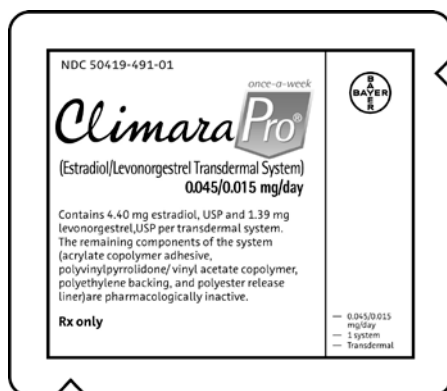
**Inactive ingredient:** acrylate copolymer adhesive, and polyvinylpyrrolidone/vinyl acetate copolymer.

### Instructions for Use

**Climara Pro** (Klī-mār-uh prō)  
(estradiol transdermal system)

Read this Patient Information before you start using Climara Pro 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 Pro.

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

### Step 2. Remove the Climara Pro 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.

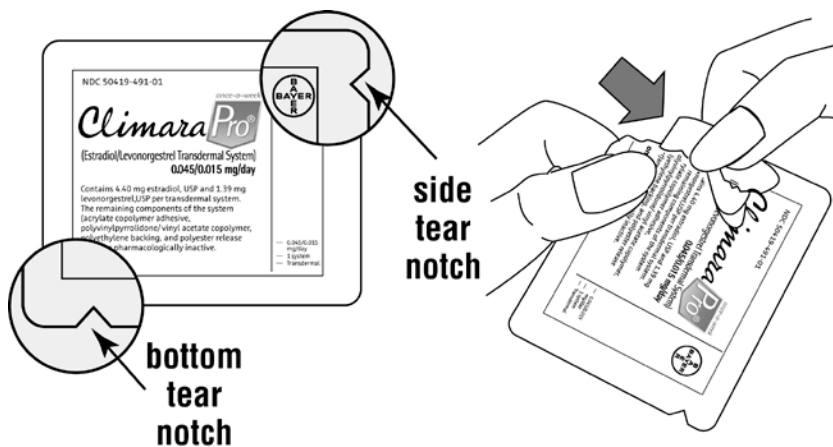


Figure B

**Step 3. Remove the adhesive liner. See Figure C**

- You will see that Climara Pro 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**

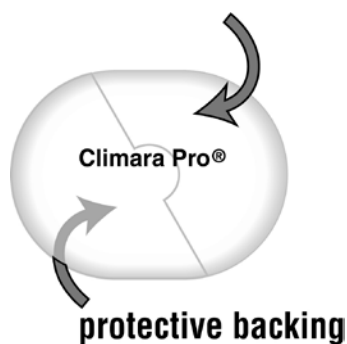


Figure C

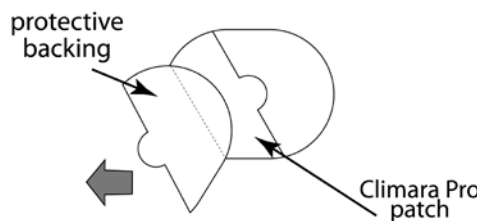


Figure D

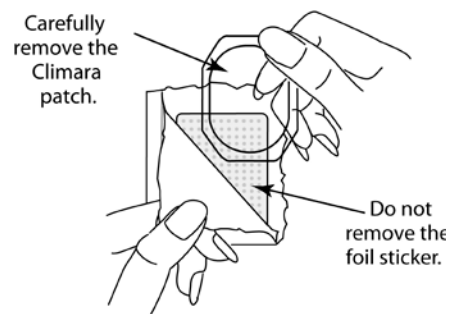


Figure E

**Step 4. Placing the patch on your skin.**

- Apply the sticky side of the patch to one of the areas of skin shown below. **See Figure F and Figure G**
- **Do not** touch the sticky side of the patch with your fingers.



**Figure F**

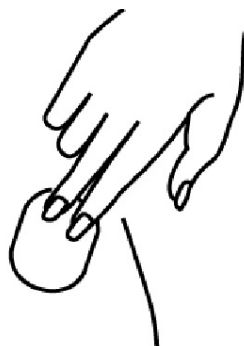
**Figure G**

**Note:**

- Avoid the waistline, since clothing and belts may cause the patch to be rubbed off.
- Do not apply Climara Pro to your breasts.
- Only apply Climara Pro 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 Pro 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.

**This label may not be the latest approved by FDA.  
For current labeling information, please visit <https://www.fda.gov/drugsatfda>**

- 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. Do not flush used patches in the toilet.

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

Revised: 8/2021

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

Made In USA

Manufactured for:  
Bayer HealthCare Pharmaceuticals Inc.  
Whippany, NJ 07981

Manufactured by:  
Kindeva Drug Delivery L.P.  
Northridge CA, 91324