

## PRODUCT MONOGRAPH

### **PrCLIMARA PRO®**

(Estradiol-17 $\beta$  and Levonorgestrel) Transdermal System

45/15  $\mu$ g/day

Estrogen + Progestin

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### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	transdermal system / 45 $\mu$ g/day estradiol- 17 $\beta$ and 15 $\mu$ g/day levonorgestrel	acrylate copolymer adhesive and polyvinylpyrrolidone/vinyl acetate copolymer  <i>For a complete listing see <b>DOSAGE FORMS, COMPOSITION AND PACKAGING</b> section.</i>

#### INDICATIONS AND CLINICAL USE

CLIMARA PRO (estradiol/levonorgestrel transdermal system) is indicated for the relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states.

CLIMARA PRO is recommended for use only in patients with an intact uterus since the regimen includes a progestin whose role is to prevent endometrial hyperplasia.

#### CONTRAINDICATIONS

Estrogen/progestin combinations are contraindicated in patients with any of the following conditions:

- Liver dysfunction or disease as long as liver function tests have failed to return to normal
- Known or suspected estrogen-dependent or progestin-dependent neoplasia (eg, endometrial cancer)
- Endometrial hyperplasia.
- Known, suspected, or past history of breast cancer.
- Undiagnosed abnormal genital bleeding

- Known or suspected pregnancy
- Lactation
- Active or past history of arterial thromboembolic disease (e.g., stroke, myocardial infarction, coronary heart disease)
- Classical migraine
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis
- A high risk of venous or arterial thrombosis, including known thrombophilic disorders (see **WARNINGS AND PRECAUTIONS**)
- Partial or complete loss of vision due to ophthalmic vascular disease
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin therapy* (n=16,608) and oral estrogen-alone therapy (n=10,739) in postmenopausal women aged 50 to 79 years (1-3).

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) an increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone (MPA, 2.5 mg/day) acetate for 5.2 years compared to those receiving placebo (1).

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo (2).

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the approved indication.

## Carcinogenesis and Mutagenesis

### *Breast Cancer*

Available epidemiological data indicate that the use of combined *estrogen plus progestin* by postmenopausal women is associated with an increased risk of invasive breast cancer.

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo) (1).

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs 1.5 cm [0.9], respectively; P=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter (3).

In the *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo (2).

It is recommended that estrogens with or without progestins not be given to women with existing breast cancer or those with a previous history of the disease (see **CONTRAINDICATIONS**).

There is a need for caution in prescribing estrogens with or without progestins for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/or atypical hyperplasia at breast biopsy).

Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

*Instructions for regular self-examination of the breasts should be included in this counselling.*

### ***Ovarian Cancer***

Some recent epidemiological studies have found that the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

### ***Endometrial hyperplasia and endometrial carcinoma***

Estrogens, unopposed by progestins, increase the risk of endometrial hyperplasia/carcinoma in postmenopausal women with intact uteri. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. CLIMARA PRO (estradiol/ levonorgestrel transdermal system) provides plasma levonorgestrel

levels within the therapeutic range necessary to counteract the effects of estradiol on the endometrium.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding.

### **Pituitary Tumours**

Close medical supervision (including periodic measurement of prolactin levels) is necessary if the patient suffers from hyperprolactinemia, prolactinoma, or is at risk of developing prolactinoma.

### **Cardiovascular**

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women (1, 4, 5). The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women (1, 2).

#### ***WHI trial findings***

In the combined estrogen plus progestin arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo) (1).

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on estrogen-alone therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD (2).

#### ***HERS and HERS II findings***

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg oral medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years (5).

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD (4).

### ***Blood Pressure***

Women using HRT sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

### **Ear/Nose/Throat**

Estrogens should be used with caution in patients with otosclerosis.

### **Endocrine and Metabolism**

#### ***Glucose and lipid metabolism***

A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and postmenopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

Women with familial hypertriglyceridemia need special surveillance. Lipid- lowering measures are recommended additionally, before treatment is started.

#### ***Heme Metabolism***

Women with porphyria need special surveillance.

#### ***Calcium and phosphorus metabolism***

Because the prolonged use of estrogens with or without progestins influences the metabolism of calcium and phosphorus, estrogens with or without progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

#### ***Hypothyroidism***

Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see **DRUG INTERACTIONS - Drug-Laboratory Test Interactions**).

#### ***Vaginal Bleeding***

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt diagnostic measures to rule out the possibility of uterine malignancy, and the treatment should be re-evaluated.

### ***Uterine leiomyomata***

Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

### ***Endometriosis***

Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

## **Hematologic**

### ***Venous thromboembolism***

Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism (1).

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism (2).

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index > 30 kg/m<sup>2</sup>) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking. The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens with or without progestins should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

## **Hepatic/Biliary/Pancreatic**

### ***Gallbladder diseases***

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

### ***Hepatic hemangioma***

Particular caution is indicated in women with hepatic hemangiomas as estrogens may cause an exacerbation of this condition.

### ***Jaundice***

Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

### ***Liver function tests***

Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see the section under **Monitoring and Laboratory Tests**.

### **Immune**

#### ***Angioedema***

Exogenous estrogens may induce/exacerbate symptoms of angioedema, in particular in women with hereditary angioedema. Discontinuation of this medication should be considered.

#### ***Systemic lupus erythematosus***

Particular caution is indicated in women with system lupus erythematosus.

### **Neurologic**

#### ***Cerebrovascular insufficiency***

Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness should discontinue medication.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be re-evaluated.

#### ***Dementia***

Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women age 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study, a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline (6, 7).

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo) (6).

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance (7).

When data from the *estrogen plus progestin* arm of the WHIMS and the *estrogen-alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on estrogen plus progestin or estrogen-alone versus 23 on placebo) (7).

### ***Epilepsy***

Particular caution is indicated in women with epilepsy, as estrogens with or without progestins may cause an exacerbation of this condition.

### **Renal**

#### ***Fluid retention***

Estrogens with or without progestins may cause fluid retention.

Therefore, particular caution is indicated in cardiac, renal dysfunction or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

### **Skin**

#### ***Contact Sensitization***

Contact sensitization is known to occur with topical applications. Although it is extremely rare, patients who develop contact sensitization to any component of the patch should be warned that a severe hypersensitivity reaction may occur with continuing exposure to the causative agent.

### **Special Populations**

#### ***Pregnant Women***

CLIMARA PRO must not be used during pregnancy and lactation (see **CONTRAINDICATIONS**). If pregnancy occurs during medication with CLIMARA PRO, treatment must be discontinued immediately.

### **Monitoring and Laboratory Tests**

Before CLIMARA PRO (estradiol/levonorgestrel transdermal system) is administered, the patient should have a complete physical examination, including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should

be performed. Endometrial biopsy should be done when indicated. Baseline tests should include mammography, measurement of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess medical response to treatment. Thereafter, examinations should be made at intervals of at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

*The importance of regular self-examination of the breasts should be discussed with the patient.*

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

See **WARNINGS AND PRECAUTIONS** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combinations in general:

**Blood and lymphatic system disorders:** Altered coagulation tests (see **DRUG INTERACTIONS - Drug-Laboratory Test Interactions**).

**Cardiac disorders:** Palpitations; increase in blood pressure (see **WARNINGS AND PRECAUTIONS**); coronary thrombosis.

**Endocrine disorders:** Increased blood sugar levels; decreased glucose tolerance.

**Eye disorders:** Neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses.

**Gastrointestinal disorders:** Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating).

**General disorders and administration site conditions:** Fatigue; changes in appetite; changes in body weight; change in libido.

**Hepatobiliary disorders:** Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

**Musculoskeletal and connective tissue disorders:** Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

**Nervous system disorders:** Aggravation of migraine episodes; headaches; dizziness; neuritis.

**Psychiatric disorders:** Mental depression; nervousness; irritability.

**Renal and urinary disorders:** Cystitis; dysuria; sodium retention; edema.

**Reproductive system and breast disorders:** Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea ; vaginal itching/discharge; dyspareunia; endometrial hyperplasia;

pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.

**Skin and subcutaneous tissue disorders:** exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema; chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.

**Vascular disorders:** Isolated cases of: thrombophlebitis; thromboembolic disorders; exacerbations of varicose veins.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The most commonly reported adverse reaction to CLIMARA PRO (estradiol/levonorgestrel transdermal system) in clinical trials was skin irritation at the application site. In controlled clinical trials, discontinuation due to application site reaction occurred in 1.5% of subjects receiving CLIMARA PRO for up to 3 cycles (vs. 3.2% of placebo subjects) and in 8.3% of subjects receiving CLIMARA PRO for up to 13 cycles.

If adverse symptoms persist, the prescription of HRT should be re-considered.

## **DRUG INTERACTIONS**

### **Overview**

Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.

Preparations inducing liver enzymes (e.g., barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens. The extent of interference with transdermally administered estradiol and levonorgestrel is not known.

### **Drug-Drug Interactions**

#### **Effects of other drugs on CLIMARA PRO**

##### ***Substances increasing the clearance of sex hormones (diminished efficacy by enzyme induction)***

Estrogens are metabolized partially by cytochrome P450 enzymes (e.g. CYP 3A4). Interactions can occur with drugs that induce CYP enzymes which can result in increased clearance of sex hormones and which may lead to changes in the uterine bleeding profile and/or reduction of the therapeutic effect.

CYP enzyme inducers include phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort.

### ***Substances with variable effects on the clearance of sex hormones***

When co-administered with sex hormones, many HIV protease inhibitors (e.g., nelfinavir, ritonavir, ritonavir-boosted protease inhibitors), HCV protease inhibitors (e.g., boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine) can increase or decrease plasma concentrations of the estrogen. These changes may alter the safety and effectiveness of CLIMARA PRO. Healthcare providers should refer to the label of the individual anti-HIV/HCV protease inhibitor or non-nucleoside reverse transcriptase inhibitor for further drug-drug interaction information.

### ***Substances decreasing the clearance of sex hormones (enzyme inhibitors)***

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen.

### **Drug-Lifestyle Interactions**

Acute alcohol ingestion during use of HRT may lead to elevations in circulating estradiol levels.

### **Drug-Herb Interactions**

It was found that some herbal products (e.g., St. John's wort) which are available as OTC products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be aware of other non-prescription products concomitantly used by the patient, including herbal and natural products obtained from the widely spread health stores.

### **Drug-Laboratory Test Interactions**

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- increased sulfobromophthalein retention;
- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;
- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone ( $T_4$ ) as measured by column or radioimmunoassay; free  $T_3$  resin uptake is decreased, reflecting the elevated TBG; free  $T_4$  concentration is unaltered.
- other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged;
- reduced response to the METOPIRONE test;

- impaired glucose tolerance;
- reduced serum folate concentration;
- increased serum triglycerides and phospholipid concentration.

Following four consecutive weekly applications of CLIMARA PRO, mean ( $\pm$  SD) SHBG concentrations (C<sub>min</sub>) declined from a predose value of 47.5 (25.8) to 41.2 (22.4) nmol/L at week 4. In a 1-year clinical trial conducted with 45  $\mu$ g estradiol/30  $\mu$ g levonorgestrel and 45  $\mu$ g estradiol/40  $\mu$ g levonorgestrel transdermal systems, there were no clinically significant changes in fibrinogen or thrombin-antithrombin III complex values in either treatment group. In a 4-week clinical trial conducted with 45  $\mu$ g estradiol/30  $\mu$ g levonorgestrel and 45  $\mu$ g estradiol/40  $\mu$ g levonorgestrel transdermal systems, mean serum levels of SHBG and CBG at week 4 were decreased by about 20% in comparison to their respective baseline values, while no differences were observed in protein binding of either estradiol or levonorgestrel between weeks 1 and 4.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks.

The pathologist should be informed that the patient is receiving estrogen/progestin therapy when relevant specimens are submitted.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

Patients should be reevaluated within 3 to 6 months after initiation of treatment, to assess response to treatment.

### **Recommended Dose and Dosage Adjustment**

**Combination estrogen/progestin regimens are indicated for women with an intact uterus.** CLIMARA PRO (estradiol/levonorgestrel transdermal system) delivers 45  $\mu$ g estradiol and 15  $\mu$ g levonorgestrel per day, and is worn continuously on the abdomen or buttocks. A new system should be applied once a week during each 28-day cycle. Irregular uterine bleeding may occur, particularly in the first 6 months, but generally decreases with time, and eventually may lead to an amenorrheic state.

### ***Initiation of Therapy***

Women not currently using continuous estrogen or combination estrogen/progestin therapy may start therapy with CLIMARA PRO at any time. However, women currently using continuous estrogen or combination estrogen/progestin therapy should complete the current cycle of therapy before initiating CLIMARA PRO therapy. Women often experience bleeding at the completion of the cycle. The first day of this bleeding would be an appropriate time to begin CLIMARA PRO therapy.

### **Administration**

#### ***Patch Application***

The physician should discuss the most appropriate placement of the patch with the patient. Immediately after removal of a patch from the pouch and removal of one-half of the protective

liner, the adhesive side of the CLIMARA PRO patch should be placed on a clean, dry area of intact skin, and the remaining one-half of the protective liner peeled off. The area selected should not be oily, damaged or irritated, and not exposed to the sun. The area selected should also be one at which little wrinkling of the skin occurs during movement of the body, preferably the buttocks, lower abdomen or hip. The patch may also be placed on the side or lower back. The patch should be placed consistently on the same area of the body with each application (e.g., either the buttocks, lower abdomen, hip, side or lower back). Experience to date has shown that less irritation of the skin occurs on the buttocks than on other sites of application. Therefore, it is advisable to apply CLIMARA PRO to the buttocks. The waistline should be avoided, since tight clothing may dislodge the patch. Application to areas where sitting would dislodge the patch should also be avoided. The patch should be pressed firmly in place, making sure there is good contact, especially around the edges. If the patch lifts, pressure should be applied to maintain adhesion.

In the event that a patch should fall off, it can be reapplied to another area of the buttocks, lower abdomen, hip, side or lower back. If it fails to adhere then a new patch should be applied. In either case, the original treatment schedule should be continued. Patches should not be applied to the same skin site twice in succession. **CLIMARA PRO must not be applied to the breasts to avoid potentially harmful effects on the breast tissue.**

### **Missed Dose**

If the patient forgets to apply the patch, she should be counseled to apply a new patch and continue with her regular treatment schedule.

### **OVERDOSAGE**

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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### **Symptoms of overdose**

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Progestin overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

### **Treatment of overdose**

In the event of a possible overdose, the system(s) should be removed immediately and symptomatic treatment should be given.

## ACTION AND CLINICAL PHARMACOLOGY

### **Mechanism of Action**

CLIMARA PRO (estradiol/levonorgestrel transdermal system) is a transdermal system containing estradiol-17 $\beta$  (estrogen) and levonorgestrel (progestin) intended for continuous administration as hormone replacement therapy. Following once-weekly application to intact skin, CLIMARA PRO provides continuous, controlled delivery of estradiol-17 $\beta$  and levonorgestrel to the systemic circulation.

### **Pharmacokinetics**

When given orally, estrogens and their esters are extensively metabolized by the liver (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated weaker estrogens. This results in limited oral potency.

In contrast, because the skin metabolizes estradiol only to a small extent, the transdermal administration of estradiol produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates. CLIMARA PRO maintains the favourable estradiol/estrone ratio associated with transdermal application, which is comparable to that observed in premenopausal women during the early follicular phase.

Transdermal administration of estradiol offers several advantages over oral administration. It avoids the hepatic "first pass" effect thereby minimizing interpatient and inpatient variations due to variable hepatic metabolism. Transdermal administration also avoids gastrointestinal intolerance associated with oral administration of estrogens.

### ***Absorption***

Administration of CLIMARA PRO to postmenopausal women 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, and are sustained for the entire patch wear period. A summary of estradiol, estrone and levonorgestrel pharmacokinetic parameters after CLIMARA PRO single and multiple applications is shown in [Table 1](#) and [Table 2](#).

**Table 1: Summary of mean ( $\pm$  SD) pharmacokinetic parameters following a single application of CLIMARA PRO in 24 healthy postmenopausal women**

Parameter	Units	Estradiol	Estrone	Levonorgestrel
C <sub>max</sub>	pg/mL	54.3 $\pm$ 18.9	43.9 $\pm$ 14.9	138 $\pm$ 51.8
T <sub>max</sub> *	hours	42	84	90
AUC	pg C h/mL	6340 $\pm$ 1740	6890 $\pm$ 2520	22900 $\pm$ 8860

\* T<sub>max</sub> is expressed as the median value.

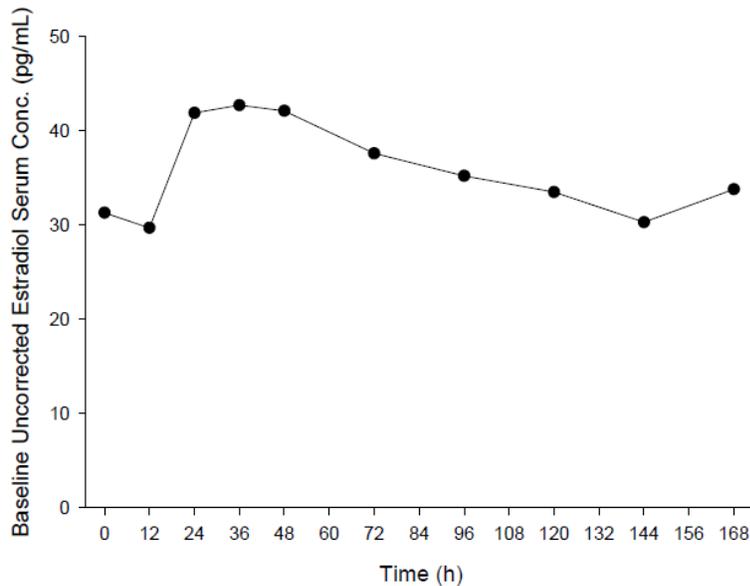
**Table 2: Summary of mean ( $\pm$  SD) pharmacokinetic parameters (week 4) following four consecutive weekly applications of CLIMARA PRO in 44 healthy postmenopausal women**

Parameter	Units	Estradiol	Estrone	Levonorgestrel
Cmax	pg/mL	50.7 $\pm$ 28.6	81.6 $\pm$ 252	194 $\pm$ 111
Tmax*	hours	36	48	48
Cmin	pg/mL	33.8 $\pm$ 28.7	72.5 $\pm$ 253	153 $\pm$ 69.6
AUC	pg C h/mL	6002 $\pm$ 1919	7642 $\pm$ 10518	27948 $\pm$ 16426

\* Tmax is expressed as the median value.

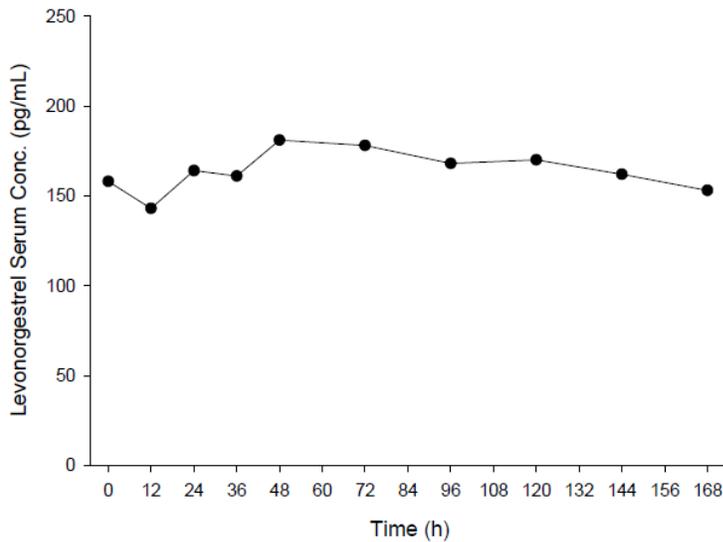
At steady state, CLIMARA PRO maintains an average serum estradiol concentration of about 36 pg/mL during the application period, as depicted in [Figure 1](#).

**Figure 1: Mean estradiol concentration profile (week 4) following four consecutive weekly applications of CLIMARA PRO**



Following the application of CLIMARA PRO, levonorgestrel concentrations reach a maximum in about 3 days. At steady state, CLIMARA PRO maintains an average serum levonorgestrel concentration of about 166 pg/mL during the application period, as depicted in [Figure 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 sex hormone binding globulin (SHBG) and albumin. In a multiple dose study with CLIMARA PRO, about 57-58% of estradiol was bound nonspecifically to serum albumin and about 40-41% to SHBG. The fraction of unbound estradiol in blood was less than 2%.

Levonorgestrel in serum is bound to both SHBG and albumin. In a multiple dose study with CLIMARA PRO, less than 2% of levonorgestrel was found to circulate in blood unbound. Approximately 77-79% was strongly bound to SHBG and 19-22% to albumin.

### ***Metabolism***

The biotransformation of transdermally administered estradiol is the same as that of the endogenous hormone. Estradiol is mainly metabolized in the liver but also extrahepatically, e.g., in the gut, kidney, skeletal muscles and target organs. These processes involve the formation of estrone, estriol, catecholestrogens and sulfate and glucuronide conjugates of these compounds, which are all distinctly less estrogenic or even nonestrogenic. After transdermal administration, the metabolism of estradiol to estrone and conjugates remains within the physiological range as seen during the early follicular phase in the reproductive period, indicated by an estradiol/estrone serum level ratio of approximately 1.

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.

### ***Excretion***

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Following patch removal, serum estradiol concentrations decline rapidly with a mean terminal half-life of  $3.0 \pm 0.67$  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.

### ***Estrogen Pharmacology***

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol-17 $\beta$  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  $\mu\text{g}$  of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism.

Administration of transdermal estradiol to postmenopausal women elevates plasma estradiol concentrations into the range observed in premenopausal women at the early to mid-follicular stage. As a result of the increased plasma estradiol concentrations, plasma concentrations of FSH and LH are decreased and vaginal cytology is converted to a pattern resembling that found in premenopausal women, with improvement of the maturation and karyopyknotic indices.

Loss of ovarian estradiol-17 $\beta$  production after menopause can result in instability of thermoregulation, causing hot flashes associated with sleep disturbance and excessive sweating. Estrogen replacement therapy is effective in reducing the number and intensity of hot flashes associated with menopause.

## ***Progestin Pharmacology***

Levonorgestrel is a 19-nortestosterone derivative with potent progestogenic effects, but no significant estrogenic activity. It has been established that the inclusion of either cyclic or continuous administration of a progestin, such as levonorgestrel, in hormone replacement therapy inhibits endometrial proliferation induced by estrogen. This inhibition of endometrial proliferation is associated with a reduction in risk of endometrial hyperplasia and the attendant risk of carcinoma in women with intact uteri. Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen.

## **STORAGE AND STABILITY**

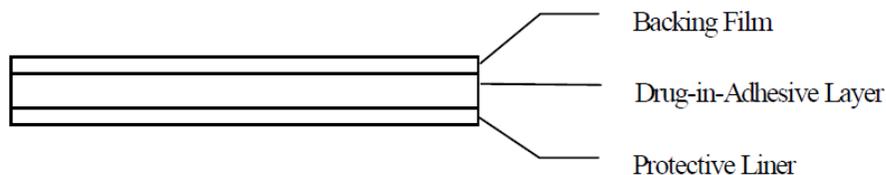
Store between 15°C and 30°C in sealed pouch. Do not refrigerate or freeze. Apply immediately upon removal from the protective pouch.

**Keep out of the reach of children and pets before and after use.**

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

Each translucent 22 cm<sup>2</sup> system contains 4.55 mg of estradiol hemihydrate, Ph. Eur. (equivalent to 4.40 mg of estradiol-17β) and 1.39 mg of levonorgestrel, USP, Ph. Eur., and provides controlled delivery of estradiol-17β 45 μg/day and levonorgestrel 15 μg/day to the patient. Available in packages of 4 systems.

The CLIMARA PRO system is composed of 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, and (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 system are estradiol and levonorgestrel. The nonmedicinal components of the system (acrylate copolymer adhesive and polyvinylpyrrolidone/vinyl acetate copolymer) are pharmacologically inactive.

## PART II : SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

#### Estradiol-17 $\beta$

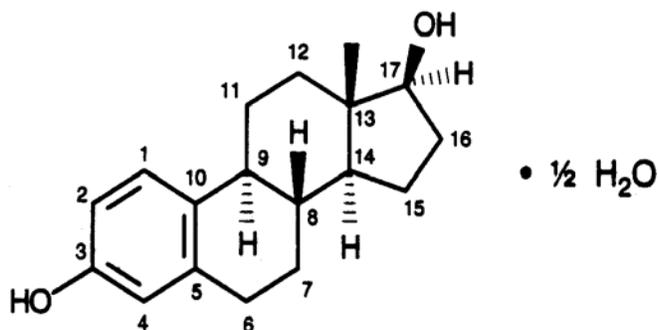
Common Name: Estradiol hemihydrate, Ph. Eur.

Chemical Name: Estra-1,3,5(10)-triene-3,17 $\beta$ -diol, hydrate (2:1) (CAS 9 CI)

Molecular Formula:  $C_{18}H_{24}O_2 \cdot \frac{1}{2}H_2O$

Molecular Weight: 281.40

Structural Formula:



Physical form: White to off-white crystals or crystalline powder

Melting point: 173°C to 180°C

Solubilities: Practically insoluble in water, freely soluble in alcohol, and soluble in acetone, dioxane and other organic solvents.

## Levonorgestrel

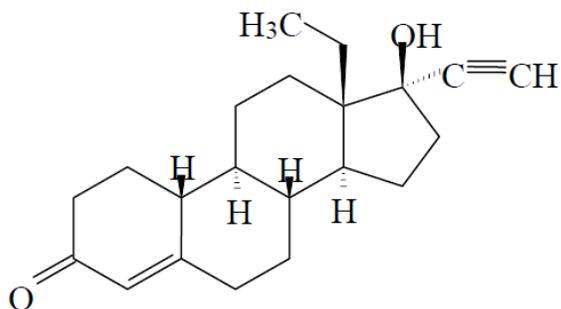
Common Name: levonorgestrel, USP, Ph. Eur.

Chemical Name: 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17'' $\alpha$ )-(—)

Molecular Formula: C<sub>21</sub> H<sub>28</sub> O<sub>2</sub>

Molecular Weight: 312.45

Structural Formula:



Physical Form: White to off-white crystalline powder

Melting Point: 232°C to 239°C

Solubilities: Practically insoluble in water, and slightly soluble in ethanol, vegetable oils, chloroform, ether and alkaline solutions.

## CLINICAL TRIALS

### Pivotal Clinical Trials

Although different strengths of levonorgestrel were tested, for the purpose of endometrial protection against hyperplasia, the 45  $\mu$ g estradiol/15  $\mu$ g levonorgestrel transdermal system has been determined to deliver enough levonorgestrel to obtain adequate protection against endometrial hyperplasia, and the higher strengths are therefore not justified.

### *Study Results*

#### *Effect on vasomotor symptoms*

The efficacy of a 45  $\mu$ g estradiol/30  $\mu$ g levonorgestrel (E<sub>2</sub> 45  $\mu$ g/LNG 30  $\mu$ g) transdermal system in the relief of vasomotor symptoms in postmenopausal women was demonstrated in a double-blind, randomized, placebo-controlled trial. The system was administered continuously for three 28-day cycles, with a new system applied weekly. The mean weekly number of hot flashes (primary efficacy variable) was statistically significantly reduced from baseline at Weeks 4, 8 and 12 and at All Endpoints as compared to baseline (intent-to-treat population). Pairwise comparisons showed statistically significant differences for the E<sub>2</sub> 45  $\mu$ g/LNG 30  $\mu$ g group versus the placebo group at all timepoints. The severity of hot flashes was evaluated by analysis

of mean decrease from baseline in daily maximum severity on Days 1, 2, 3, 4, 5, 6 and 7 of each cycle. The E<sub>2</sub> 45 µg/LNG 30 µg group had statistically significant decreases in severity from baseline at all timepoints. CLIMARA PRO (E<sub>2</sub> 45 µg/LNG 15 µg) and the E<sub>2</sub> 45 µg/LNG 30 µg strength used in this study have been shown to be bioequivalent in terms of estradiol delivery.

**Table 3: Mean changes in weekly number and daily maximum severity of hot flushes at All Endpoints<sup>1</sup> (Vasomotor Symptoms study)**

	E <sub>2</sub> 45 µg/LNG 30 µg (n=92)	Placebo (n=88)
Mean weekly number of hot flushes at baseline	88.17	93.83
Mean weekly number of hot flushes at All Endpoints	16.22	54.64
Mean change from baseline in weekly number of hot flushes at All Endpoints	-72.02 <sup>2,3</sup>	-37.74
Mean daily maximum severity of hot flushes at baseline (on Day 7 of run-in period)	2.90	2.84
Mean change from baseline in mean daily maximum severity <sup>4</sup> of hot flushes at All Endpoints (on Day 7 of patch wear period)	-2.12 <sup>2,3</sup>	-0.61

- 1 Final evaluation on study medication carried forward to 12 weeks
- 2 Statistically significant vs. placebo (p< 0.001)
- 3 Statistically significant vs. baseline (p < 0.001)
- 4 1 = mild, 2 = moderate, 3 = severe

In the 1-year endometrial protection study, an analysis of the results of the first three cycles of treatment in a symptomatic subset of women confirmed the efficacy of CLIMARA PRO (E<sub>2</sub> 45 µg/LNG 15 µg). The mean total number of weekly hot flushes (intent-to-treat population) was statistically significantly reduced (p<0.001) from baseline at each cycle with continuous administration of CLIMARA PRO, and was similar to the results seen with unopposed transdermal estrogen (E<sub>2</sub> 45 µg). The CLIMARA PRO group also showed statistically significant decreases in mean daily maximum severity of hot flushes at each cycle.

### ***Effects on the endometrium***

In a randomized, double-blind, multicentre, 1-year clinical trial of 412 postmenopausal women (with intact uteri) treated with a continuous regimen of CLIMARA PRO or with a continuous estradiol-only transdermal system, results of evaluable endometrial biopsies showed that no hyperplasia was seen with CLIMARA PRO. [Table 4](#) below summarizes these results (intent-to-treat populations).

**Table 4: Incidence of endometrial hyperplasia during continuous combined treatment with CLIMARA PRO (intent-to-treat population)**

	CLIMARA PRO (E <sub>2</sub> 45µg/LNG 15 µg) (n=210)	Estradiol (E <sub>2</sub> 45 µg) (n=201)
No. of patients with biopsies at β 6 months <sup>1</sup>	124	139
No. of patients with biopsies at 1 year <sup>2</sup>	102	110
No. (%) of patients with hyperplasia <sup>3</sup>	0 (0%)	19 (17.3%)
95% Confidence Interval	0 - 3.55%	9.75 - 24.79%
p-value <sup>4</sup>	<0.001	

1 Defined as β 180 days of treatment.

2 Defined as β 323 days of treatment.

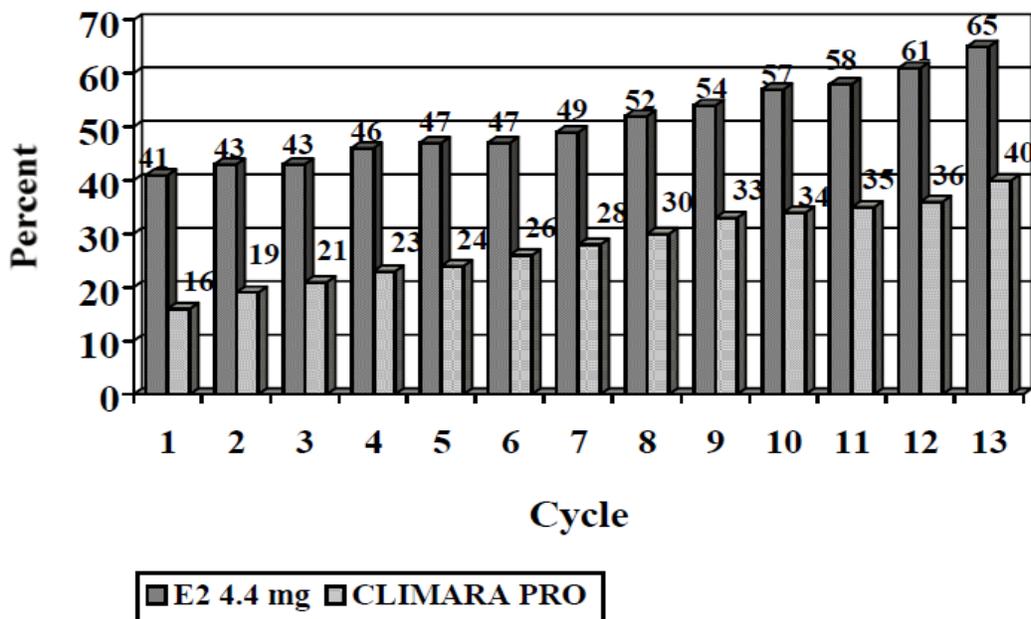
3 Includes hyperplasia occurring at any time after initiation of treatment as a proportion of patients with biopsies at one year.

4 P-value for comparison to unopposed estradiol dose using the Fisher Exact test. P-values were adjusted by the method of Bonferroni:  $p < 0.0167$ .

### *Effects on uterine bleeding or spotting*

The effects of CLIMARA PRO on uterine bleeding or spotting were evaluated in the 1-year endometrial protection 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 number of subjects at each cycle with data. Last non-missing cycle carried forward through cycle 13. Bleeding associated with endometrial biopsies not included.

### *Effect on lipids*

In the 1-year endometrial protection trial, CLIMARA PRO significantly ( $p < 0.001$ ) decreased total cholesterol and triglycerides compared to continuous transdermal estradiol alone. CLIMARA PRO also decreased low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) compared to estradiol alone (see [Table 5](#)).

**Table 5: Mean % change from baseline lipid profile: values after 1 year of treatment**

Lipid Parameter	Estradiol 45 µg (n=204)	CLIMARA PRO (E2 45 µg/LNG 15 µg) (n=212)
Total cholesterol	-1.5%	-6.5%
Triglycerides	1.2%	-18.5%
LDL-C	-3.2%	-5.6%
HDL-C	1.6%	-4.3%

### *Effect on coagulation parameters*

Effects on coagulation parameters were assessed following one year of treatment with E<sub>2</sub> 45 µg/LNG 30 µg (n=23) and E<sub>2</sub> 45 µg/LNG 40 µg (n=26) transdermal systems. No clinically significant changes were observed for fibrinogen and thrombin-antithrombin III complex (TAT).

### *Effect on skin sensitization*

A twenty-one day cumulative irritation study conducted in 29 postmenopausal females compared the skin irritation potential of CLIMARA PRO with that of a placebo patch containing only the adhesive. Both patches showed only minimal to low irritation potential.

The sensitization potential of CLIMARA PRO and a placebo patch containing adhesive only was assessed in 170 postmenopausal females. The study consisted of a three-week induction phase, a 10 to 17 day rest period, and a one-week challenge phase. None of the subjects showed any sensitization-type reactions.

## **TOXICOLOGY**

A guinea pig sensitization study was conducted with CLIMARA PRO (estradiol/levonorgestrel transdermal system) and a placebo patch containing only the adhesive. No positive responses were observed during the challenge phase of this study, indicating that CLIMARA PRO does not induce contact sensitization in this model.

Observations after repeated dermal administration of CLIMARA PRO (estradiol/levonorgestrel transdermal system) to rats once weekly for 4 weeks (29 to 30 days of continuous exposure) were primarily exaggerated pharmacological effects that are expected following high doses of estradiol and levonorgestrel in rodents. No unexpected toxic effects were observed. Slight to moderate local irritation was observed for both CLIMARA PRO and the hormone-free placebo patch containing adhesive only, and was shown to be reversible after patch removal.

No signs of local intolerance were observed following topical application of CLIMARA PRO or a hormone-free placebo patch to the skin of rabbits for 4 hours.

Neither the CLIMARA PRO patch nor the hormone-free placebo patch was shown to induce contact sensitization in the guinea pig.

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 (**See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS**).

Long-term continuous administration of natural and synthetic progestins increases the frequency of benign liver tumours in male mice, but not in male or female rats.

In vitro and in vivo studies with estradiol or with levonorgestrel gave no indication of a mutagenic potential.

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## INFORMATION FOR THE PATIENT

This leaflet describes the uses of estrogens and progestins, precautions to take when using these hormones and how to use CLIMARA PRO. Please read it carefully. If you want to know more or have any questions, please ask your doctor or pharmacist.

### **Serious Warnings and Precautions**

The Women's Health Initiative (WHI) trial is a large clinical study that assessed the benefits and risks of oral combined *estrogen plus progestin* therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, invasive breast cancer, pulmonary emboli (blood clots in the lungs) and deep venous thrombosis (blood clots in the leg veins) in postmenopausal women taking oral combined *estrogen plus progestin*.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone*.

Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke, and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- Estrogens with or without progestins should not be used for prevention of heart disease or stroke.
- Estrogens with or without progestins should be used prescribed at the **lowest effective dose** and for the **shortest period of time** possible. Regular medical follow-up is advised.

### **INTRODUCTION: What is CLIMARA PRO?**

The CLIMARA PRO transdermal system (patch) is a hormone replacement therapy (HRT) that contains the hormone estrogen (estradiol), the same hormone that is produced naturally in the body, as well as a progestin, levonorgestrel. A CLIMARA PRO patch is worn continuously for one week on the abdomen or buttocks, and provides continuous, controlled delivery of 45 µg estradiol and 15 µg levonorgestrel per day, through the skin into the bloodstream. A new patch should be applied once a week during each 28-day cycle.

CLIMARA PRO should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your doctor. You should regularly talk with your doctor regularly about whether you still need treatment with HRT.

## **INDICATIONS**

CLIMARA PRO is approved to provide relief from the symptoms of menopause.

### **Uses of Estrogens**

When a woman's menstrual periods cease (menopause) around the age of 50, the ovaries stop producing estrogens, the main female hormones. Sometimes the ovaries are removed by an operation causing "surgical menopause". When the amount of estrogen produced by the body begins to decrease, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes"). Hot flashes can cause frequent awakening at night, with sleep disturbance leading to fatigue, irritability, and depression. The use of estrogen replacement can stop or greatly reduce the occurrence of menopausal flushes.

As a result of estrogen deficiency, changes also occur in and around the vagina (causing itching, burning, dryness, painful intercourse) and urethra (causing difficulty or burning on urination, and frequent urination). These changes may improve with estrogen therapy.

### **Uses of Progestins**

Progestins used in hormone replacement therapy have similar effects to the female sex hormone progesterone. During child bearing years, progesterone is responsible for regulation of the menstrual cycle. The estradiol delivered by CLIMARA PRO not only relieves your menopausal symptoms, but, like estrogens produced by your body, may also stimulate growth of the inner lining of the uterus, the endometrium. In menopausal and postmenopausal women with an intact uterus, stimulation of growth of the endometrium may result in irregular bleeding. In some cases this may progress into a disorder of the uterus known as endometrial hyperplasia (overgrowth of the lining of the uterus). Endometrial hyperplasia increases the risk of endometrial cancer (cancer of the lining of the uterus). The risk of endometrial hyperplasia is reduced if a progestin medication, such as levonorgestrel, is given together with estrogen replacement therapy.

If you have had a hysterectomy (surgical removal of the uterus), endometrial hyperplasia cannot occur and administration of a progestin is not necessary. Therefore, CLIMARA PRO **should not** be used by women who have had a hysterectomy.

## RESTRICTIONS ON USE: WHO SHOULDN'T USE CLIMARA PRO

You **should not** use CLIMARA PRO if you:

- Have active liver disease.
- Have a personal history of breast cancer or endometrial cancer (cancer of the lining of the uterus).
- Have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus).
- Have experienced undiagnosed or abnormal genital bleeding.
- Have a history of heart attack, heart disease or stroke.
- Experience migraine headaches.
- Have a personal history of blood clots or active thrombophlebitis (inflammation of the veins).
- Are at high risk of having a blood clot, including if you were born with certain blood clotting disorders.
- Have had partial or complete loss of vision due to blood vessel disease of the eye.
- Are pregnant or think you may be pregnant. (Since pregnancy may be possible early in menopause while you are still having spontaneous periods, the use of non-hormonal birth control should be discussed with your doctor at this time. If you take estrogen during pregnancy, there is a small risk of your unborn child having birth defects).
- Are breastfeeding.
- Have had a hysterectomy (surgical removal of the uterus).
- Have had an allergy (hypersensitivity) to estradiol, levonorgestrel or unusual reaction to estrogen, progestin or to any component of the other ingredients in CLIMARA PRO (see **PHARMACEUTICAL INFORMATION** section of this leaflet).

## WARNINGS AND PRECAUTIONS

See the **Boxed Warnings** on the front page.

### **Overgrowth of the lining of the uterus and cancer of the uterus**

The use of *estrogen alone* therapy by post-menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

The purpose of adding a progestin medication to estrogen therapy is to reduce the risk of endometrial hyperplasia.

You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with your doctor. You should also report any unexpected or unusual vaginal bleeding to your doctor.

If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy. Therefore, CLIMARA PRO should not be used by women who have had a hysterectomy.

## **Breast Cancer**

The results of the WHI trial indicated an increased risk of breast cancer in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer.

In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting HRT.

Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor. The use of HRT may make it more difficult to detect breast cancer by mammography, in some cases.

**Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women.** You should review technique for breast self-examination with your doctor.

## **Ovarian Cancer**

In some studies, the use of *estrogen-alone* and *estrogen plus progestin* therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

## **Heart Disease and Stroke**

The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

Your doctor may recommend that you temporarily discontinue taking hormone replacement therapy in advance of expected hospitalizations or surgery.

## **Abnormal Blood Clotting**

The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life threatening or cause serious disability.

## **Gallbladder disease**

The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

## **Dementia**

The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in post-menopausal women age 65 and over taking oral combined estrogen plus progestin compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral estrogen-alone compared to women taking placebo.

## **Skin Sensitivity**

Contact sensitization (extreme sensitivity of the skin) has been known to occur with the use of topical applications (medications which are applied to the skin). Although it is extremely rare, patients who develop contact sensitization to any component of the patch may have a severe hypersensitivity reaction (i.e. allergic reaction) with continued use of the patch.

## **Precautions**

Certain medical conditions may be aggravated by estrogens or progestins. Therefore, these hormones should either not be used at all or should be used with caution under these conditions.

To help your doctor decide whether you should use CLIMARA PRO and what precautions should be taken during use, tell your doctor if you:

- have a history of allergy or intolerance to any medications or other substances
- are undergoing surgery or need long bed rest
- have a history of liver disease; jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have a history of endometrial hyperplasia (overgrowth of the lining of the uterus);
- have been diagnosed with high prolactin levels or prolactinoma;
- have experienced undiagnosed or abnormal vaginal bleeding;
- have a history of migraine headaches;
- have a personal or family history of blood clots or a personal history of heart attack, heart disease or stroke
- have a personal history of thrombophlebitis (inflammation of veins);
- have had partial or complete loss of vision due to blood vessel disease of the eye;
- are pregnant or may be pregnant;
- are breastfeeding;
- have had a hysterectomy (surgical removal of the uterus);
- smoke;
- have a history of kidney disease, asthma or epilepsy (seizures);
- have a history of bone disease (this includes metabolic conditions or cancers that can affect blood levels of calcium and phosphorus);
- have a history of high blood pressure;
- have been diagnosed with diabetes;

- have been diagnosed with porphyria (a disease of blood pigment)
- have a history of high cholesterol or high triglycerides (a fat-like substance in the blood);
- have a history of uterine fibroids (non-cancerous growths of the uterus) or endometriosis (growth outside of the uterus made up of tissues that line the uterus);
- have a history of depression.
- have been told that you have a condition called hereditary angioedema or if you have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage), or digestive tract
- have been diagnosed with hearing loss due to otosclerosis
- have been diagnosed with lupus

Tell your doctor if you are taking any other medications, including prescription and non-prescription medications, over-the-counter medications, vitamins or herbal products. There are some medicines which may interfere with the effects of CLIMARA PRO and CLIMARA PRO may interfere with the effects of other medicines.

Drugs that may interact with CLIMARA PRO include:

- anticoagulants, antidiabetic agents
- drugs used for the treatment of certain heart diseases or high blood pressure (eg, diltiazem, verapamil)
- drugs used for the treatment of HIV infections and Hepatitis C Virus infections (e.g., nelfinavir, ritonavir-boosted protease inhibitors, boceprevir, telaprevir, nevirapine)
- barbiturates, hydantoin, carbamazepine, meprobamate, phenylbutazone, primidone, phenytoin, oxcarbazepine, topiramate, felbamate or rifampicin
- antibiotics (eg, erythromycin, clarithromycin, penicillin, tetracycline)
- antifungals (eg, griseofulvin, fluconazole, itraconazole, ketoconazole, voriconazole)
- antivirals (ritonavir)

Alcohol, grapefruit juice and St. John's wort may also interact with CLIMARA PRO.

## **ADVERSE EFFECTS**

See also the **WARNINGS AND PRECAUTIONS** section of this leaflet.

The following side effects have been reported in women taking estrogen-progestin combinations (such as CLIMARA PRO). Check with your doctor if you develop any of these symptoms:

- retention of fluid
- migraine headaches
- localized darkening of the skin
- breast tenderness and/or excessive vaginal secretions (may be a sign that too much estrogen is taken)
- persistent upper abdominal pain, nausea, vomiting, tender abdomen (may be signs of gallbladder disease)

- lower abdominal pain or swelling, painful and/or heavy periods (may be signs of growth of fibroids in the uterus)
- yellowing of the eyes or skin (may be signs of jaundice)
- upper abdominal pain or swelling (may be signs of liver tumours)
- mood swings
- changes in body weight

Estrogens produced outside the body may cause or worsen symptoms of swelling in body parts such as hands, feet, face, and airway passages.

In addition, CLIMARA PRO may produce some redness or irritation under or around the patch in some women (see [Helpful Hints](#)).

Check with your doctor as soon as possible if any of the following occur:

- irregular or unusual vaginal bleeding
- changes in speech
- dizziness and faintness
- vomiting
- intolerable breast tenderness
- breast enlargement or lumps
- severe headaches
- changes in vision
- persistent or severe skin irritation
- fluid retention or bloating persisting for more than 6 weeks

Check with your doctor immediately if you experience:

- trouble breathing or tightness of the chest
- severe pain in one or both legs or numbness suddenly affecting one side or one part of the body
- sudden change in vision
- first migraine headache
- skin redness, warmth, swelling, tenderness, pain or hardening of tissue around a vein
- pain or heaviness in the legs or chest
- sudden shortness of breath
- coughing of blood
- rapid pulse or dizziness
- any other unusual symptom

These are not all of the possible side effects of estrogen/progestin therapy. If you experience any side effects or for more information, contact your doctor or your pharmacist.

## HOW TO USE CLIMARA PRO

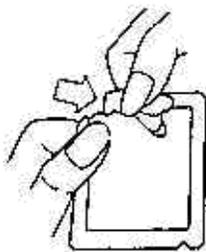
### How CLIMARA PRO Works

The CLIMARA PRO patch contains both estradiol and levonorgestrel. When applied to the skin as directed below, CLIMARA PRO continually releases small, controlled amounts of estradiol and levonorgestrel, which pass through the skin into the bloodstream. Estradiol provides relief from menopausal symptoms and levonorgestrel provides important protection for your uterus (See [Uses of Progestins](#)).

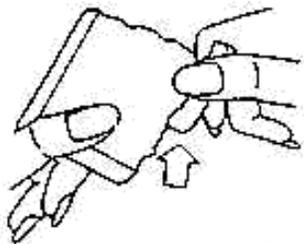
Each CLIMARA PRO patch is individually sealed in a protective pouch. A protective liner covers the adhesive side of the patch - the side that will be placed against your skin. This liner must be removed before applying the patch. See below for instructions on how to apply CLIMARA PRO.

### How to Apply CLIMARA PRO

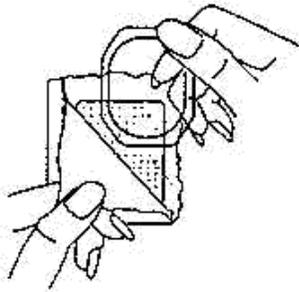
Never cut the pouch with scissors – you might damage the patch inside. To open the pouch, hold it vertically with the CLIMARA PRO name facing you. Tear the pouch at the notch provided at the top of the left-hand corner, tearing from left to right.



Next, open the right side of the pouch using the notch at the bottom of the right-hand corner and tear from bottom to top.

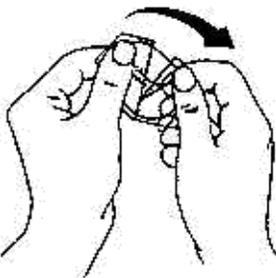


Carefully remove the patch.

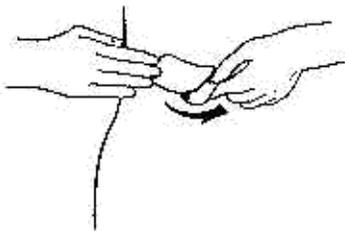


A protective plastic backing covers the adhesive side of the patch and must be removed before applying it. The patch itself is oval and translucent.

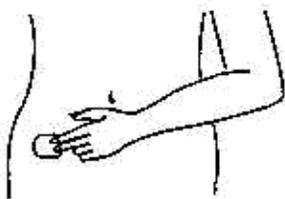
Peel off one side of the protective backing. Try to avoid touching the adhesive side of the patch.



Using the other half of the backing as a handle, apply the sticky side of the patch to the skin. Peel away the other side of the backing and press the entire patch firmly to the skin (see [Where to Apply CLIMARA PRO](#), below). Discard the protective backing.

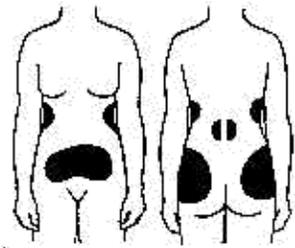


Apply firm pressure around the edges for about 10 seconds to make sure there are no air bubbles under the patch. If the patch lifts, pressure should be applied to maintain adhesion.



### ***Where to Apply CLIMARA PRO***

Apply the adhesive side of the patch to a clean dry area of the skin on the sides, lower back or abdomen of your body or buttocks. **Do not apply CLIMARA PRO to your breasts due to potentially harmful effects on the breast tissue.** Avoid the waistline, since tight clothing may rub and remove the patch. Application to areas where sitting would dislodge the patch should also be avoided. The sites of application in the chosen body area (for example, buttocks) must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. Apply the patch immediately after opening the pouch and removing the protective liner (see [How to Apply CLIMARA PRO](#), above). Press the patch firmly in place with the fingers for about 10 seconds, making sure there is good contact, especially around the edges. If the patch lifts, pressure should be applied to maintain adhesion.



CLIMARA PRO should be worn continuously for one week. You may wish to experiment with different locations when applying a new patch, to find ones that are most comfortable for you and where clothing will not rub on the patch.

### ***When to Apply CLIMARA PRO***

The CLIMARA PRO patch should be changed once weekly. When changing the patch, remove the used CLIMARA PRO patch. Carefully fold it in half so that it sticks to itself, because used patches still contain active hormones, and throw it away, safely out of the reach of children or pets. Any adhesive that might remain on your skin can be easily rubbed off. Then place the new CLIMARA PRO patch on a different skin site. (The same skin site should not be used again for at least 1 week after removal of the patch).

Contact with water when you are bathing, swimming or showering should not affect the patch. In the unlikely event that a patch should fall off, you may reapply the same patch to a new area of skin and continue with your regular schedule. Make sure that there is good contact, especially around the edges. If the patch will not stick completely to your skin, then apply a new patch to a new area of skin for the remainder of the 7-day dosing interval. **Do not apply two patches at the same time.**

Once in place, the patch should not be exposed to the sun for prolonged periods of time.

### **How CLIMARA PRO is supplied**

CLIMARA PRO is supplied in boxes containing 4 patches.

## **Helpful Hints**

**What to do if the patch falls off.** Should a patch fall off in a very hot bath or shower, shake the water off the patch. Dry your skin completely and try to reapply the patch to a new site and continue your regular schedule. If it still does not stick, then apply a **new** patch to a new site and continue with your regular schedule.

In addition, there are some other causes for the patch failing to stick. If you are having patches fall off regularly, this could be happening as a result of:

- using any type of bath oil
- using soaps with a high cream content
- using skin moisturizers before applying the patch

Patch adhesion may be improved if you avoid using these products, and by cleansing the site of application with rubbing alcohol before you apply the patch.

### **What to do if your skin becomes red or irritated under or around the patch.**

As with any product that covers the skin for a period of time (such as bandages), the CLIMARA PRO patch can produce some skin irritation in some women. This varies according to the sensitivity of each woman.

Usually this redness does not pose any health concern to you, but to reduce this problem, there are some things that you may do:

- Choose the buttocks as the site of application
- Change the site of application of the CLIMARA PRO patch every time a new patch is applied, usually once weekly

If redness and/or itching continues, you should consult your doctor.

### **Always Remember**

Your doctor has prescribed CLIMARA PRO for you after a careful review of your medical needs. Use it only as directed and do not give it to anyone else. Your doctor should re-examine you at least once a year.

If you have any questions, contact your doctor or pharmacist.

## **OVERDOSE**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Symptoms:** Overdosage with estrogen or progestin containing products may cause nausea, breast discomfort, fluid retention, bloating, vaginal bleeding, depressed mood, tiredness, acne and hirsutism (excessive hair growth).

**Treatment:** If you think you have taken an overdose of CLIMARA PRO, remove the patch(es) immediately.

## **MISSED DOSE**

If you forget to apply a patch, then apply a new patch and continue with your regular treatment schedule.

## **PHARMACEUTICAL INFORMATION**

The medicinal ingredients in CLIMARA PRO are estradiol and levonorgestrel. CLIMARA PRO also contains the non-medicinal ingredients acrylate copolymer adhesive and polyvinylpyrrolidone/vinyl acetate copolymer.

## **STORAGE**

CLIMARA PRO patches should be stored at room temperature, between 15°C and 30°C. Do not refrigerate or freeze. Apply CLIMARA PRO immediately upon removal from the protective pouch. **Do not store the patches out of the pouch.**

CLIMARA PRO should be kept out of the reach of children and pets before and after use.

## **REPORTING SUSPECTED SIDE EFFECTS**

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:

- Fax to 1-866-678-6789 (toll-free), or

- Mail to: Canada Vigilance Program

Health Canada, Postal Locator 0701E

Ottawa, ON

K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

**NOTE:** Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

## MORE INFORMATION

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For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or **canada.medinfo@bayer.com**.

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.bayer.ca> or by contacting the manufacturer at the above mentioned phone number and email address.

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