PRODUCT MONOGRAPH

PrCLIMARA® 25
PrCLIMARA® 50
PrCLIMARA® 75
PrCLIMARA® 100

estradiol hemihydrate transdermal system

(estradiol-17β)

0.025 mg/day
0.05 mg/day
0.075 mg/day
0.1 mg/day

Estrogen

Bayer Inc.
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estradiol hemihydrate transdermal system

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Product Information Summary

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
topical	transdermal system / 0.025 mg/day 0.05 mg/day 0.075 mg/day 0.1 mg/day	acrylate copolymer (consisting of isooctyl acrylate, acrylamide, vinyl acetate copolymer), ethyl oleate, glyceryl monolaurate, isopropyl myristate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

CLIMARA (estradiol hemihydrate transdermal system) is indicated for:

- the relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states.

CLIMARA 50, 75 and 100 are indicated for:

- the prevention of osteoporosis in naturally occurring or surgically induced estrogen-deficiency states. In post-menopausal women already diagnosed as having osteoporosis and vertebral fractures, treatment with CLIMARA may retard further bone loss.

CLIMARA 25 is not indicated for the prevention of osteoporosis.

When CLIMARA is prescribed solely for the prevention of postmenopausal osteoporosis, it is to be considered in light of other available therapies. Adequate diet, calcium and vitamin D intake, cessation of smoking as well as regular physical weight bearing exercise are required in addition to the administration of CLIMARA.

CLIMARA should be prescribed with an appropriate dosage of a progestin for women with intact uteri, in order to prevent endometrial hyperplasia/carcinoma.

CONTRAINDICATIONS

CLIMARA (estradiol hemihydrate transdermal system) should not be used in individuals with any of the following conditions:

- 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.
- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Known or suspected estrogen-dependent malignant neoplasia (e.g. endometrial cancer).
- Endometrial hyperplasia.
- Known, suspected, or past history of breast cancer.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy or lactation.
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Active or past history of confirmed venous thromboembolism (such as deep vein 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.
- Presence or history of liver tumours (benign or malignant)

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) indicated 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 acetate (MPA, 2.5 mg/day) 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]

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar.

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.
- For the prevention of osteoporosis, Climara (estradiol hemihydrate transdermal system) should be considered in light of other available therapies.

General

The effects of CLIMARA on the ability to drive and use machines have not been studied.

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 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 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. HRT increases the density of mammographic images which may adversely affect the radiological detection of breast cancer in some cases.

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 combined estrogen plus progestin 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 epidemiologic 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

Estrogen-only HRT increases the risk of endometrial hyperplasia if taken by women with intact uteri.

Estrogen should be prescribed with an appropriate dosage of progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

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 recurring abnormal vaginal bleeding.

Pituitary Tumors

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 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.[4]

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.[5]

Blood pressure

Women using hormone replacement therapy 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 post-menopausal 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 hyperlipidemias 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 influences the metabolism of calcium and phosphorus, estrogens 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-Laboratory Test Interactions**).

Genitourinary

Vaginal bleeding

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate 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^2) 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 trauma. 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 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 disease

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 exacerbation of this condition.

Jaundice

Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops, or if there is a recurrence of cholestatic pruritis which first occurred during pregnancy or during previous use of sex steroids, 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**.

Hepatic Tumours

Benign hepatic adenomas have been associated with the use of combined estrogen and progestin oral contraceptives. Although benign and rare, these tumours may rupture and cause death from intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestin preparations, but they should be considered if abdominal pain and tenderness, abdominal mass, or hypovolemic shock occurs in patients receiving estrogen. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives. The causal relationship of this malignancy to these drugs is not known.

Immune

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

Systemic lupus erythematosus

Particular caution is indicated in women with systemic 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 reevaluated.

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 (WHIMS), 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 HRT may cause an exacerbation of this condition.

Renal

Fluid retention

Estrogens may cause fluid retention. Therefore, particular caution is indicated in cardiac or 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.

Special Populations

Estrogens should be used with caution in patients with chorea minor.

Pregnant women: If pregnancy occurs during medication with CLIMARA, treatment should be withdrawn immediately.

Skin

Persistent erythema or pruritis at the application site may occur.

Estrogens should be used with caution in patients with chloasma, or a history or chloasma gravidarum.

Dermatologic sensitivity

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.

Monitoring and Laboratory Tests

Before CLIMARA 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 only 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 three to six months after initiation of treatment to assess 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.

Liver function tests should be done periodically in subjects who are suspected of having hepatic disease.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

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

Blood and lymphatic system disorders

Altered coagulation tests (see **WARNINGS AND PRECAUTIONS, 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.

Immune system disorders

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

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

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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse 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.

Table 1 – Adverse events occurring at rate of ≥ 1% reported in CLIMARA phase III clinical trials[*] R-838T-010[33] R-838T-011[34] in the indication: relief of menopausal symptoms.

Reported adverse event	Incidence (%)			
	Climara 50 (n=201)	Climara 100 (n=194)	Premarin[**] (n=136)	Placebo patch (n=72)
Cardiac disorders				
syncope	1.0	0.0	0.0	1.4
palpitation	1.0	1.5	1.3	1.5
Ear and labyrinth disorders:				
earache	2.0	1.0	2.2	0.0
tinnitus	0.5	1.0	0.7	0.0
Eye disorders:				
vision abnormal	2.0	0.5	0.7	1.4
Gastrointestinal disorders:				
abdominal pain	10.9	16.0	14.7	8.3
nausea	5.5	6.2	4.4	2.8
vomiting	3.0	8.2	11.8	5.6
flatulence	3.5	6.7	3.7	1.4
constipation	3.0	2.6	0.0	1.4
dyspepsia	2.0	1.0	0.0	0.0
hemorrhoids	0.0	1.0	0.0	1.4

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Reported adverse event	Incidence (%)			
	Climara 50 (n=201)	Climara 100 (n=194)	Premarin[**] (n=136)	Placebo patch (n=72)
General disorders and administration site conditions:				
edema	12.9	10.3	5.1	5.6
pain	8.5	10.8	2.9	6.9
malaise	5.0	2.6	4.4	6.9
rigors	3.0	3.1	1.5	0.0
fatigue	2.0	1.5	3.7	0.0
chest pain	1.0	2.1	0.7	5.6
Immune system disorders				
allergic reactions	2.5	0.5	2.2	0.0
Infections and infestations:				
infection viral	10.0	8.8	10.3	9.7
infection fungal	4.0	2.6	1.5	1.4
infection bacterial	1.0	1.5	0.0	0.0
infection	1.5	0.5	0.0	1.4
herpes zoster	1.0	0.5	0.0	0.0
Investigations:				
weight increase	3.0	3.1	1.5	0.0
Musculoskeletal and connective tissue disorders:				
back pain	8.0	9.3	3.7	5.6
arthralgia	5.5	4.6	2.2	2.8
myalgia	2.0	2.1	2.2	1.4
leg cramps	0.5	2.6	4.4	0.0
arthritis	1.0	1.5	0.0	0.0
arthrosis	1.5	0.5	1.5	0.0
fracture, accidental	0.0	2.1	1.5	0.0
myostasis	1.0	0.0	0.0	0.0
Nervous system disorders:				
headache	17.9	13.4	22.8	9.7
dizziness	3.0	2.6	2.9	2.8
hyperesthesia	2.0	1.0	2.2	1.4
sweating increased	2.0	0.0	0.0	0.0
Psychiatric disorders:				
depression	5.5	8.2	6.6	0.0
insomnia	2.5	2.1	0.7	0.0
anxiety	2.0	2.1	2.2	0.0
nervousness	2.0	1.0	0.0	1.4
somnolence	0.0	1.5	0.0	0.0
amnesia	0.0	1.0	0.0	0.0

Table 1 – Adverse events occurring at rate of ≥ 1% reported in CLIMARA phase III clinical trials* R-838T-010[33] R-838T-011[34] in the indication: relief of menopausal symptoms.

Reported adverse event	Incidence (%)			
	Climara 50 (n=201)	Climara 100 (n=194)	Premarin** (n=136)	Placebo patch (n=72)
Renal and urinary disorders:				
urinary tract infection	3.0	3.1	0.7	1.4
polyuria	0.5	1.0	1.5	2.8
dysuria	0.5	1.0	0.0	1.4
cystitis	1.0	0.0	0.7	1.4
urinary incontinence	1.0	0.0	0.0	0.0
Reproductive system and breast disorders:				
breast pain	8.0	28.9	13.2	4.2
leukorrhea	6.5	7.2	2.9	1.4
vaginitis	4.0	5.2	2.2	0.0
pelvic pain	1.0	3.6	2.9	2.8
breast malformation	0.5	1.5	0.7	0.0
vaginal disorder	1.0	1.0	0.0	0.0
Respiratory, thoracic and mediastinal disorders				
upper respiratory tract infection	16.9	17.0	26.5	8.3
pharyngitis	3.0	7.2	5.1	2.8
rhinitis	4.0	5.7	2.9	1.4
sinusitis	4.0	5.2	5.9	2.8
coughing	2.0	2.6	2.9	0.0
bronchitis	3.0	1.0	0.7	0.0
respiratory disorder	1.0	0.5	0.7	0.0
laryngitis	1.0	0.0	0.0	0.0
Skin and subcutaneous tissue disorders:				
dermatitis	4.0	5.7	3.7	4.2
pruritus	6.0	3.1	3.7	5.6
rash	2.5	0.5	0.7	4.2
urticaria	1.5	0.5	0.0	1.4
sweating increased	1.0		0.0	0.0
acne	0.5	1.0	2.9	1.4
rash, etythematous	0.0	1.5	0.7	0.0
rash, pustular	0.0	1.0	0.0	0.0
skin cold and clammy	0.5	1.0	0.0	0.0
Vascular disorders				
hypertension	1.0	3.1	0.0	0.0

* Both clinical trials R-838T-010[33] and R-838T-011[34] were double-blind, randomized, parallel, active- and placebo- controlled, multiple-dose (3 x 3 week treatment cycles, separated by 1 week washout) studies.

** 0.625 mg conjugated estrogen tablets, administered daily

The most commonly reported adverse event reported in CLIMARA (estradiol hemihydrate transdermal system) clinical trials R-838T-010[33] and R-838T-011[34] were abdominal pain (10.9% for CLIMARA 50, 16.0% for CLIMARA 100, 14.7% for Premarin, 8.3% for placebo), viral infection (10.0% for CLIMARA 50, 8.8% for CLIMARA 100, 10.3% for Premarin, 9.7% for placebo), edema (12.9% for CLIMARA 50, 10.3% for CLIMARA 100, 5.1% for Premarin, 5.6% for placebo), headache (17.9% for CLIMARA 50, 13.4% for CLIMARA 100, 22.8% for Premarin, 9.7% for placebo), breast pain (8.0% for CLIMARA

50, 28.9% for CLIMARA 100, 13.2% for Premarin, 4.2% for placebo) and upper respiratory tract infection (16.9% for CLIMARA 50, 17.0% for CLIMARA 100, 26.5% for Premarin, 8.3% for placebo). The overall rate of discontinuation due to application site irritation was 6.8% (7.9% for the CLIMARA 50 system and 5.3% for the CLIMARA 100 system) compared to 11.5% for the placebo system.

In a further randomized, controlled, two-year clinical trial (Study 308-3B[30]) comparing CLIMARA with placebo, the overall rate of application site reactions with CLIMARA was 28.7%, compared to 17.4% for the placebo system; the dropout rate due to application site reactions during the period was 4.7% (6 out of 129 subjects), compared to 0% for the placebo system.

Overall, the most commonly reported adverse reaction to CLIMARA in clinical trials was breast pain and application site irritation.

Post-Market Adverse Drug Reactions

Adverse events occurring post-market with CLIMARA are consistent with those reported during clinical trials.

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, meprobamate, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens. The extent of interference with transdermally administered estradiol-17ß is not known.

Drug-Drug Interactions

Effects of other drugs on CLIMARA

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 (eg, nelfinavir, ritonavir, ritonavir-boosted protease inhibitors), HCV protease inhibitors (eg, boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (eg, nevirapine) can increase

or decrease plasma concentrations of the estrogen. These changes may alter the safety and effectiveness of CLIMARA. 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 or the progestin or both, and may result in side effects.

Drug-Food Interactions

Grapefruit juice is an inhibitor of cytochrome P450 (CYP 3A4) [32] and could therefore increase plasma concentrations of estrogens, which might result in side effects.

Drug-Herb Interactions

It was found that some herbal products (e.g. St. John's wort) which are available as over-the-counter (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 made 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, adrenal, renal and liver function tests may be affected by estrogen-containing products:

- 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 (T4) as measured by column or radioimmunoassay; T3 resin uptake is decreased, reflecting the elevated TBG; free T4 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;
- impaired glucose tolerance;
- increased serum triglycerides and phospholipids concentration;

With transdermally administered estradiol-17ß, no effect on fibrinogen, antithrombin III, TBG, CBG or SHBG nor decreases in serum triglycerides have been observed.

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 hormone replacement therapy when relevant specimens are submitted.

Drug-Lifestyle Interactions

Interaction with alcohol

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

CLIMARA (estradiol hemihydrate transdermal system) should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma. Progestin therapy is not required as part of hormone replacement therapy in women who have had a previous hysterectomy.

Use of estrogen, alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., 3- to 6-month intervals) to determine if treatment is still necessary. For women who have intact uteri, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Recommended Dose and Dosage Adjustment

CLIMARA should be applied once a week and worn on a continuous basis for 7 days. It should be removed and a new one applied after 7 days. Only one patch should be worn at any one time during the 7-day dosing interval.

Initiation of Therapy

Four CLIMARA systems are available: CLIMARA 25 (0.025 mg/day), CLIMARA 50 (0.05 mg/day), CLIMARA 75 (0.075 mg/day) and CLIMARA 100 (0.1 mg/day). Treatment is usually initiated with CLIMARA 50 applied to the skin once weekly. The dose should be adjusted as necessary to control symptoms.

Clinical response at the lowest effective dose should be the guide for establishing administration of CLIMARA. The necessity for hormone replacement therapy for menopausal symptoms should be re-assessed periodically. Attempts to taper or discontinue the medication should be made at 3- to 6-month intervals.

For the prevention of osteoporosis, CLIMARA 50 (0.05 mg/day) is the minimum dose approved. The choice of which dose to use should be made on the basis of individual considerations such as the age of the patient, other risk factors for osteoporosis and response to therapy as assessed by biochemical markers.

Missed Dose

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

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 the protective liner, the adhesive side of the CLIMARA patch should be placed on a clean, dry area of intact skin. The area selected should not be oily, damaged or irritated, and not exposed to the sun. The site 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 to the buttocks. The waistline should be avoided, since tight clothing may dislodge the patch. The patch should be pressed firmly in place with the palm of the hand, making sure there is good contact, especially around the edges.

In the event that a patch should fall off, a new one should be applied and the original treatment schedule should be continued. Patches should not be applied to the same skin site twice in succession.

CLIMARA must not be applied to the breasts in order to avoid potentially harmful effects on the breast tissue.

OVERDOSAGE

For management of a suspected overdose, contact your regional Poison Control Centre

Symptoms

Overdosage with transdermal application of estradiol is unlikely. 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.

Treatment

Symptomatic treatment should be given and the CLIMARA patch(es) should be removed.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

CLIMARA (estradiol hemihydrate transdermal system) is composed of a translucent polyethylene film with an acrylate adhesive matrix containing estradiol-17β. Upon application to intact skin, CLIMARA provides continuous systemic delivery of estrogen by releasing estradiol-17β, the major estrogenic hormone secreted by the human ovary.

Pharmacodynamics

Estradiol-17β is the predominant estrogen produced by the ovaries in premenopausal women. 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 follicle-stimulating hormone and luteinizing hormone are decreased and vaginal cytology is converted to a pattern resembling that found in premenopausal women, with improvement of the maturation and karyopyknotic indices. Estrogens are effective in reducing the number and intensity of hot flushes associated with menopause and in the prevention of osteoporosis.

Pharmacokinetics

Absorption

CLIMARA provides controlled delivery of approximately 0.025, 0.05, 0.075 or 0.1 mg of estradiol per day into the systemic circulation, depending on the strength of the system.

Distribution and Metabolism

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 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 some advantages over oral administration. It avoids the hepatic "first-pass" effect thereby minimizing interpatient and intrapatient variations due to variable hepatic metabolism. Transdermal administration avoids gastrointestinal intolerance associated with oral administration of estrogens.

Consistent serum estradiol concentrations are maintained with CLIMARA over a one-week application interval. Linear pharmacokinetics have been demonstrated for CLIMARA. On average, CLIMARA 100 maintained mean steady state serum estradiol levels of 70 pg/mL and CLIMARA 50 maintained mean steady-state serum estradiol levels of approximately 35 pg/mL.

CLIMARA does not produce an estrogen accumulation following multiple one-week applications.

Excretion

Because estradiol has a short half-life (0.3 to 2 hours after parenteral administration), transdermal administration allows a rapid decline in blood levels after CLIMARA is removed.

Estrogen Pharmacology

Independent of the route of administration, estrogen exerts a dose-dependent stimulating effect on mitosis and proliferation of the endometrium. Unopposed estrogen increases the frequency of endometrial hyperplasia and thus the risk of endometrial carcinoma. In order to avoid endometrial hyperplasia the sequential administration of an appropriate dosage of progestin is recommended during long-term therapy in women with intact uteri.

STORAGE AND STABILITY

Store between 15ºC and 30ºC. Store in sealed pouch. Apply immediately upon removal from the protective pouch.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

CLIMARA (estradiol hemihydrate transdermal system) is available in four strengths:

CLIMARA 25: each translucent 6.5 cm^2 system contains 2.04 mg of estradiol hemihydrate, Ph. Eur. (equivalent to 2.0 mg estradiol-17β), and provides controlled delivery of estradiol-17β, 0.025 mg/day, to the patient. Available in packages of 4 systems.

CLIMARA 50: each translucent 12.5 cm^2 system contains 3.9 mg of estradiol hemihydrate, Ph. Eur. (equivalent to 3.8 mg estradiol-17β), and provides controlled delivery of estradiol-17β, 0.05 mg/day, to the patient. Available in packages of 4 systems.

CLIMARA 75: each translucent 18.75 cm^2 system contains 5.85 mg of estradiol hemihydrate, Ph. Eur. (equivalent to 5.7 mg estradiol-17β), and provides controlled delivery of estradiol-17β, 0.075 mg/day, to the patient. Available in packages of 4 systems.

CLIMARA 100: each translucent 25.0 cm^2 system contains 7.8 mg of estradiol hemihydrate, Ph. Eur. (equivalent to 7.6 mg estradiol-17β), and provides controlled delivery of estradiol-17β, 0.1 mg per day, to the patient. Available in packages of 4 systems.

CLIMARA is composed of two layers: (1) a translucent polyethylene film and (2) an acrylate adhesive matrix containing estradiol hemihydrate, Ph. Eur. A protective polyester liner is attached to the adhesive surface and must be removed before the system can be used.

Active ingredient:	estradiol hemihydrate, Ph. Eur. (estradiol-17β)
Non-active ingredients:	acrylate copolymer (consisting of isooctyl acrylate, acrylamide, vinyl acetate copolymer), ethyl oleate, glyceryl monolaurate, isopropyl myristate

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

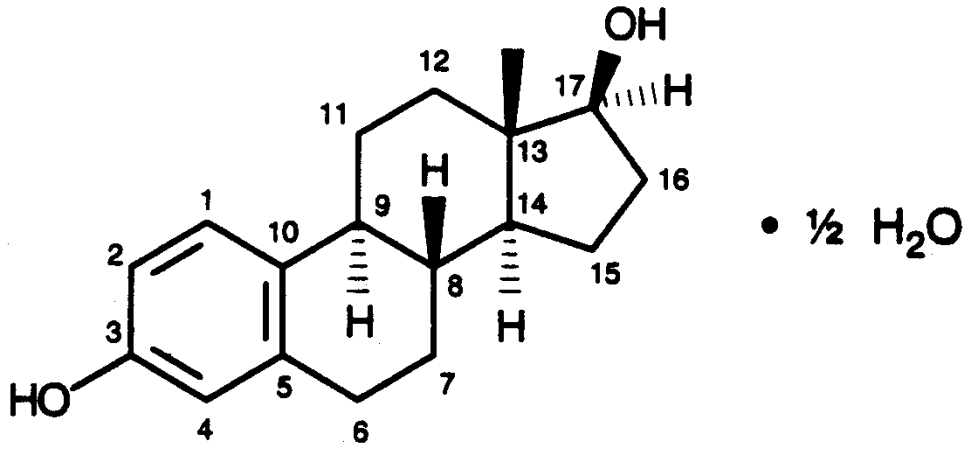
Drug Substance

Proper name: Estradiol hemihydrate, Ph. Eur.

Chemical name: Estra-1,3,5(10)-triene-3,17β-diol, hydrate (2:1) (CAS 9 CI)

Molecular formula and molecular mass: $C_{18}H_{24}O_2 \cdot ½H_2O$
281.40

Structural formula:



Physicochemical properties:

Physical form:	White to off-white crystals or crystalline powder
Melting point:	173ºC to 180ºC
pKa value:	10.71
Partition coefficient:	log P_{ow} 3.30

CLINICAL TRIALS

Clinical Trials

Seven clinical trials performed with CLIMARA patches are summarized. Premarin® was used as an active comparator in some of the clinical trials. Premarin is available for sale in Canada.

Efficacy and Safety Studies

Study Demographics and Trial Design

Table 2 – Summary of patient demographics for clinical trials in the indication: relief of menopausal symptoms

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
R-838T-010[33]	Double-blind, randomized, parallel, placebo-controlled, multiple-dose study (3 x 3 week treatment cycles, 1 week washout in between)	A: CLIMARA 50 patch + placebo patch, each 1/week B: CLIMARA 100 + placebo patch, each 1/week C: placebo patch + placebo patch, each 1/week Patches were applied to abdomen 1/week for 3 cycles (3 week treatment periods followed by 1 week washout); total study duration = 11 weeks	A: n = 72 B: n = 70 C: n = 72	A: 50.8 (26 – 71) years B: 51.5 (25 – 74) years C: 51.5 (33 – 70) years	F
R-838T-011[34]	Double-blind, randomized, parallel, active- and placebo-controlled, multiple-dose study (3 x 3 week treatment cycles, separated by 1 week washout)	A: CLIMARA 50 + placebo patch + placebo capsule B: CLIMARA 100 + placebo patch + placebo capsule C: Premarin® 0.625 mg conjugated estrogen tablets (encapsulated) + placebo patch + placebo patch patches = 1/week capsules = 1/day Patches were applied to abdomen 1/week for 3 cycles (3 week treatment periods followed by 1 week washout); total study duration = 11 weeks	A: n = 130 B: n = 124 C: n = 136	A: 50.8 (26 – 70) years B: 50.0 (28 – 73) years C: 50.7 (31 – 73) years	F

Table 2 – Summary of patient demographics for clinical trials in the indication: relief of menopausal symptoms

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
92098[35]	Double-blind, double-dummy comparative study.	A: CLIMARA 50 patch + placebo patch B: CLIMARA 100 patch + placebo patch C: placebo patch + placebo patch Each patch was applied 1/week for 4 months duration, continuously	A: n = 28 B: n = 28 C: n = 28	A: 50.6 (32 – 62) years B: 52.7 (38 – 64) years C: 52.0 (38 – 64) years	F
97074A[36]	placebo-controlled, double-blind, parallel group, randomized study.	A: CLIMARA 25 patch B: placebo patch Each patch was applied 1/week for 3 28-day cycles.	A: n = 92 B: n = 94	A: 52.1 (45-67) years B: 52.0 (44-70) years	F
97095A[37]	parallel group, double-blind, randomized, controlled study	A: CLIMARA 25 + placebo capsule B: Premarin® 0.3 mg capsule + placebo patch Each patch was applied 1/week for 3 28-day cycles.	A: n = 95 B: n = 98	A: 53.3 (44-67) years B: 50.8 (44-62) years	F

Table 3 – Summary of patient demographics for clinical trials in the indication: prevention of osteoporosis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
308-3B[30]	Parallel group, double-blind, randomized, placebo-controlled study. Two patches of different sizes were worn at all times (at least one was a placebo), in order to preserve the blinding.	A: CLIMARA 25 patch + placebo patch, 1/week for twenty-six, 28-day cycles B: CLIMARA 50 + placebo patch, 1/week for twenty-six, 28-day cycles C: CLIMARA 60* + placebo patch, 1/week for twenty-six, 28-day cycles D: CLIMARA 100 + placebo patch, 1/week for twenty-six, 28-day cycles	A: n = 129 B: n = 46	51.2 (40-71) years	F
ME 93063[38]	Parallel-group, double-blind, randomized, placebo-controlled study. Two patches of different sizes were worn at all times (at least one was a placebo), in order to preserve the blinding.	A: CLIMARA 50 patch + placebo patch, B: CLIMARA 100 + placebo patch,	A: n = 93 B: n = 48	57.4 (44-65) years	F

* CLIMARA 60 (providing controlled delivery of 0.060 mg estradiol-17β per day) is not approved for sale in Canada.

Study results

Study R-838T-010[33] was performed to compare the safety and efficacy of once-weekly applications of CLIMARA 50 and CLIMARA 100 patches with placebo in women with vasomotor symptoms.

Conclusion: In the placebo group, 50 of 72 patients completed the study. In the CLIMARA 50 group, 53 of 72 patients completed the study. In the CLIMARA 100 group, 61 of 70 patients completed the study. Both CLIMARA 50 and CLIMARA 100 were significantly ($p \leq 0.05$) more effective than placebo in reducing hot flushes; global ratings of efficacy were also generally superior to placebo. CLIMARA 100 performed consistently better than CLIMARA 50 for all efficacy parameters. Statistically significant ($p \leq 0.05$) treatment effects with both doses were seen after only 3 weeks of treatment.

Table 4 – Study R-838T-010: efficacy results

Primary Endpoints	**Associated value and statistical significance for drug at specific dosages**	**Associated value and statistical significance for placebo or active control**
Weekly Hot Flush Rate (mean ± S.D.)	CLIMARA 50 Cycle 1 (week 1-3): 26±22.0 Cycle 2 (week 5-7): 16±20.9 Cycle 3 (week 9-11): 17±21.4 All Cycles: 20±21.9 CLIMARA 100 Cycle 1 (week 1-3): 24±20.0 Cycle 2 (week 5-7): 14±16.2 Cycle 3 (week 9-11): 12±17.5 All Cycles: 16±18.6	Placebo Cycle 1 (week 1-3): 47±42.0 Cycle 2 (week 5-7): 45±47.1 Cycle 3 (week 9-11): 47±48.3 All Cycles: 46±45.6
Change in Weekly Hot Flush Rate from Baseline (mean ± S.D.)	CLIMARA 50 Cycle 1 (week 1-3): -22±28.2 Cycle 2 (week 5-7): -32±30.2 Cycle 3 (week 9-11): -31±32.9 All Cycles: -28±30.6 CLIMARA 100 Cycle 1 (week 1-3): -29±26.9 Cycle 2 (week 5-7): -39±32.9 Cycle 3 (week 9-11): -40±33.3 All Cycles: -36±31.4	Placebo Cycle 1 (week 1-3): -6±17.5* Cycle 2 (week 5-7): -8±24.0* Cycle 3 (week 9-11): -6±25.0* All Cycles: -6±22.3*
Patient Global Treatment Ratings (Global rating: 0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent)	CLIMARA 50 Cycle 1 (week 1-3): 2.1±1.2*** Cycle 2 (week 5-7): 2.3±1.3 Cycle 3 (week 9-11): 2.2±1.4 All Cycles: 2.2±1.3 CLIMARA 100 Cycle 1 (week 1-3): 2.7±1.1 Cycle 2 (week 5-7): 2.7±1.2 Cycle 3 (week 9-11): 2.6±1.3 All Cycles: 2.6±1.2	Placebo Cycle 1 (week 1-3): 1.4±1.2** Cycle 2 (week 5-7): 1.3±1.4** Cycle 3 (week 9-11): 1.2±1.4** All Cycles: 1.3±1.3**

* Mean change from baseline significantly ($p \leq 0.05$) less for placebo group than for the CLIMARA 50 and CLIMARA 100 groups.
** Mean score significantly ($p \leq 0.05$) less for the placebo group than for the CLIMARA 50 and CLIMARA 100 groups.
*** Pairwise comparison with CLIMARA 50 and CLIMARA 100 statistically significant at $p \leq 0.05$.

Study R-838T-011[34] was performed to compare the safety and efficacy of once-weekly applications of CLIMARA 50 and CLIMARA 100 patches with oral Premarin tablets (0.625 mg conjugated estrogen) in women with vasomotor symptoms.

Conclusion: In the Premarin group, 120 of 136 patients completed the study. In the CLIMARA 50 group, 101 of 130 patients completed the study. In the CLIMARA 100 group, 105 of 124 patients completed the study. All 3 treatments were effective in reducing hot flushes, across all cycles as well as during each cycle; global ratings supported these results. CLIMARA 100 performed better than CLIMARA 50 and Premarin® for all efficacy parameters evaluated. Substantial reductions in weekly mean hot flush rates were seen after only 3 weeks of therapy, for all treatment groups.

Table 5 – Study R-838T-011: efficacy results

Primary Endpoints	**Associated value and statistical significance for drug at specific dosages**	**Associated value and statistical significance for placebo or active control**
Weekly Hot Flush Rate (mean ± S.D.)	CLIMARA 50 Cycle 1 (week 1-3): 32±35.2 Cycle 2 (week 5-7): 21±28.3 Cycle 3 (week 9-11): 21±29.0 All Cycles: 25±31.4 CLIMARA 100 Cycle 1 (week 1-3): 25±24.4 Cycle 2 (week 5-7): 13±22.0 Cycle 3 (week 9-11): 11±20.5 All Cycles: 16±23.1	Premarin Tablets Cycle 1 (week 1-3): 30±30.3 Cycle 2 (week 5-7): 19±26.3 Cycle 3 (week 9-11): 17±25.2 All Cycles: 22±27.9
Change in Weekly Hot Flush Rate from Baseline (mean ± S.D.)	CLIMARA 50 Cycle 1 (week 1-3): -20±29.0 Cycle 2 (week 5-7): -32±35.3 Cycle 3 (week 9-11): -32±36.6 All Cycles: -28±34.1 CLIMARA 100 Cycle 1 (week 1-3): -26±23.5 Cycle 2 (week 5-7): -38±25.7 Cycle 3 (week 9-11): -40±29.5 All Cycles: -35±26.9	Premarin Tablets Cycle 1 (week 1-3): -23±19.0 Cycle 2 (week 5-7): -34±25.8 Cycle 3 (week 9-11): -36±27.8 All Cycles: -31±24.8
Patient Global Treatment Ratings (Global rating: 0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent)	CLIMARA 50 Cycle 1 (week 1-3): 2.2±1.1** Cycle 2 (week 5-7): 2.3±1.3* Cycle 3 (week 9-11): 2.3±1.3* All Cycles: 2.2±1.2* CLIMARA 100 Cycle 1 (week 1-3): 2.5±1.0 Cycle 2 (week 5-7): 2.7±1.1 Cycle 3 (week 9-11): 2.8±1.2 All Cycles: 2.7±1.1	Premarin Tablets Cycle 1 (week 1-3): 2.5±1.0 Cycle 2 (week 5-7): 2.4±1.1 Cycle 3 (week 9-11): 2.4±1.3 All Cycles: 2.5±1.1

* Mean score significantly ($p \leq 0.05$) less for the for the CLIMARA 50 group than for the CLIMARA 100 group.

** Mean score significantly ($p \leq 0.05$) less for the for the CLIMARA 50 group than for the CLIMARA 100 group, and, mean score significantly ($p \leq$ □0.05) less for the for the CLIMARA 50 group than for the Premarin group.

Study 92098[35] was performed to compare the efficacy of CLIMARA 50 and CLIMARA 100 and a placebo patch over a 4 month period in hysterectomized, post-menopausal women.

Conclusion: In the CLIMARA 50 + placebo group, 13 of 28 patients completed the study. In the CLIMARA 100 + placebo group, 15 of 28 patients completed the study. In the placebo + placebo group, 1 of 28 patients completed the study. A statistically significant ($p<0.05$) difference between the active and placebo group was noted in hot flush rate/night sweats (change relative to baseline) at weeks 4 and 16. The effects were variable with the other menopausal symptoms assessed (palpitations, headaches, irritability, lack of concentration, sleep disturbance, depression, joint/bone/muscle pain, vaginal dryness, loss of sex drive, urinary symptoms and lethargy). The mean number of total hot flushes/night sweats for the 4 month period experienced by patients was lower in both active groups compared to the placebo group. There was a statistically significant effect of time in this parameter in the 3 comparisons made, with the mean total number and severity of hot flushes/night sweats per month decreasing during the study.

Table 6 – Study 92098: efficacy results

Primary Endpoints	**Associated value and statistical significance for Drug at specific dosages**		**Associated value and statistical significance for Placebo or active control**	
Hot Flushes / Night Sweats (Change from baseline)	CLIMARA 50		Placebo	
	Month 1		Month 1	
	Improved	81%*	Improved	35%
	Same	19%	Same	65%
	Worse	0%	Worse	0%
	Month 2		Month 2	
	Improved	73%	Improved	83%
	Same	27%	Same	8%
	Worse	0%	Worse	8
	Month 3		Month 3	
	Improved	91%	Improved	69%
	Same	9%	Same	31%
	Worse	0%	Worse	0%
	Month 4		Month 4	
	Improved	100%*	Improved	56%
	Same	0%	Same	44%
	Worse	0%	Worse	0%
	Last Assessment – improvement:	*	Last Assessment – improvement:	n.s.
	CLIMARA 100			
	Month 1			
	Improved	73%*		
	Same	27%		
	Worse	0%		
	Month 2			
	Improved	78%		
	Same	22%		

Table 6 – Study 92098: efficacy results

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
	Worse 0% Month 3 Improved 80% Same 20% Worse 0% Month 4 Improved 77% Same 23% Worse 0% Last Assessment – improvement: *	
Total No. of Hot Flushes / Night Sweats (mean ± S.D.)	CLIMARA 50 Month 1 98.4±95.5 Month 2 28.0±53.2 Month 3 6.6±12.4 Month 4 2.4±4.6 CLIMARA 100 Month 1 49.6±53.3 Month 2 21.0±30.8 Month 3 14.8±20.6 Month 4 13.9±25.5	Placebo Month 1 151.8±129.7 Month 2 81.8±88.0 Month 3 48.1±54.5 Month 4 37.0±59.4
Severity: Mean Total Score for Hot Flushes/Night Sweats (mean ± S.D.)	CLIMARA 50 Month 1 205± 256 Month 2 50 ±104 Month 3 8 ± 12 Month 4 3 ± 6 CLIMARA 100 Month 1 87± 102 Month 2 35 ±55 Month 3 23 ± 34 Month 4 18 ± 34	Placebo Month 1 307± 306 Month 2 143 ±159 Month 3 91± 112 Month 4 61 ± 101

Table 6 – Study 92098: efficacy results

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
Global Impression of Both the Investigator and Patient Regarding the Effect of Therapy on Menopausal Symptoms	Patient's Assessment CLIMARA 50 Greatly Improved 75%** Improved 16% No Change 8% CLIMARA 100 Greatly Improved 53% Improved 38% No Change 7% Investigator's Assessment CLIMARA 50 Greatly Improved 66%** Improved 25% No Change 8% CLIMARA 100 Greatly Improved 33% Improved 53% No Change 7%	Patient's Assessment Placebo Greatly Improved 22% Improved 55% No Change 22% Investigator's Assessment Placebo Greatly Improved 11% Improved 66% No Change 22%

* Statistically significantly ($p<0.05$) different relative to placebo (ANOVA).
** Statistically significantly ($p<0.05$) different relative to placebo (Cochran-Mantel Test).
n.s. Not significant.

Study 97074A[36] was performed to determine the efficacy of CLIMARA 25 compared with placebo in decreasing the frequency and severity of hot flushes in postmenopausal women.

Conclusion: CLIMARA 25 was shown to be more effective than placebo in decreasing the frequency and severity of hot flushes in post-menopausal women.

Table 7 – Study 97074A: efficacy results

Change from Baseline in Mean Weekly Number of Hot Flushes By Treatment and Cycle						
Treatment Group		**Cycle 1**	**Cycle 2**	**Cycle 3**	**All Endpoint**	**Completers Endpoint**
Climara 25 (n=92)	n	88	87	84	89	85
	mean	-39.4	-58.6	-61.2	-60.8	-61.2
	SD	31.4	36.2	37.6	37.7	37.9
Placebo (n=94)	n	91	79	73	91	77
	mean	-36.3	-51	-49.9	-47.2	-51
	SD	77.3	100.9	110.2	100.7	108.9
	p-value	0.0171*	0.0017*	0.0003*	<0.0001*	0.0003*

* $p < 0.05$

Study 97095A[37] was performed to determine the efficacy of CLIMARA 25 compared with the daily oral administration of conjugated equine estrogens in decreasing the frequency and severity of hot flushes in postmenopausal women.

Conclusion: CLIMARA 25 was equally effective as oral conjugated equine estrogen in decreasing the frequency and severity of hot flushes in postmenopausal women.

Table 8 – Study 97095A: efficacy results

Change from Baseline in Mean Weekly Number of Hot Flushes By Treatment and Cycle						
Treatment Group		**Cycle 1**	**Cycle 2**	**Cycle 3**	**All Endpoint**	**Completers Endpoint**
Climara 25 (n=95)	n	94	88	82	94	86
	mean	-40.0	-61.2	-66.0	-65.4	-66.5
	SD	32.2	40.7	43.3	42.6	42.8
Conjugated Equine Estrogen, 0.3 mg daily (n=98)	n	95	88	86	96	87
	mean	-39.0	-62.3	-66.1	-63.1	-65.4
	SD	41.3	41.3	50.3	50.2	50.5
	p-value	0.4866	0.7858	0.7565	0.9398	0.9573

Study 308-3B[30] was performed to evaluate the efficacy of treatment utilizing four different doses of CLIMARA patches as compared to placebo, in the prevention of osteoporosis of the lumbar spine in postmenopausal, hysterectomized women.

Conclusion: Of the 175 subjects randomized, 78 withdrew from the study prematurely (17 of 32 in the CLIMARA 25 group, 12 of 31 in the CLIMARA 50 group, 9 of 31 in the CLIMARA 60 group, 13 of 31 in the CLIMARA 100 group, and 27 of 46 in the placebo group).

Treatment with all CLIMARA doses resulted in increases in mean bone mineral density (BMD) of the lumbar spine and hip at each timepoint. The mean percent increases in BMD at 24 months, relative to placebo, varied from 4.86% to 7.19% at the lumbar spine and 2.30% to 5.09% at the hip. A majority of subjects at each CLIMARA dose showed no loss of BMD of the lumbar spine. This fraction at 24 months ranged from 69% for CLIMARA 25 to 94% for the CLIMARA 50 and 90% for the CLIMARA 100 group. These results were supported by the changes in biochemical parameters, serum osteocalcin, urinary deoxypyridine and urinary pyridinoline, which showed evidence of decreased bone turnover.

Table 9 – Study 308-3B: efficacy results for lumbar spine

Bone mineral density of the lumbar spine (AP View, L2-L4): mean percent change from baseline						
Treatment Group		**6 Months**	**12 Months**	**18 Months**	**24 Months**	**Endpoint**
CLIMARA 25	n	25	20	17	16	25
	mean	1.16	2.67	3.57	2.37	2.32
	p-value[a]	0.0090 †	0.0028 †	0.0009 †	0.0008 †	<0.0001 †
CLIMARA 50	n	23	21	18	18	23
	mean	2.54	3.84	3.41	4.09	3.74
	p-value[a]	<0.0001 †	<0.0001 †	0.0001 †	<0.0001 †	<0.0001 †
CLIMARA 60**	n	24	24	22	20	25
	mean	2.02	2.97	3.02	3.28	3.45
	p-value[a]	0.0003 †	0.0014 †	0.0016 †	<0.0001 †	<0.0001 †
CLIMARA 100	n	27	24	23	21	27
	mean	3.14	3.68	4.53	4.7	5.2
	p-value[a]	<0.0001 †	<0.0001 †	<0.0001 †	<0.0001 †	<0.0001 †
Placebo	n	34	26	22	21	34
	mean	-0.78	-0.82	-0.78	-2.49	-2.33
overall p-value*		<0.0001‡	<0.0001 ‡	0.0001 ‡	<0.0001‡	<0.0001 ‡

[a] p-value for comparison of each dose against placebo; p-values were adjusted by the method of Hochberg
† P1 < 0.0412
* overall p-value obtained from model: Y=TMT INV (Y=outcome variable; TMT=treatment effect; INV=investigator effect)
‡ p < 0.05
** CLIMARA 60 (providing controlled delivery of 0.060 mg estradiol-17β per day) is not approved for sale in Canada.

Table 10 – Study 308-3B: efficacy results for total hip

Bone mineral density of the total hip: mean percent change from baseline						
Treatment Group		**6 Months**	**12 Months**	**18 Months**	**24 Months**	**Endpoint**
CLIMARA 25	n	23	18	16	14	23
	mean	0.81	1.31	0.47	0.26	0.65
	p-value[a]	0.0141 †	0.0010 †	0.0106 †	0.0202 †	0.0044 †
CLIMARA 50	n	24	22	18	18	24
	mean	1.19	2.35	2.31	2.85	2.41
	p-value[a]	0.0023 †	<0.0001 †	<0.0001 †	<0.0001 †	<0.0001 †
CLIMARA 60**	n	23	22	21	20	23
	mean	0.71	1.38	1.94	3.05	2.61
	p-value[a]	0.0176 †	0.0003 †	<0.0001 †	<0.0001 †	<0.0001 †
CLIMARA 100	n	24	22	22	21	25
	mean	0.84	1.31	2.13	2.03	1.98
	p-value[a]	0.0131 †	0.0003 †	<0.0001 †	<0.0001 †	<0.0001 †
Placebo	n	34	26	22	21	34
	mean	-0.73	-1.17	-1.89	-2.04	-1.66
overall p-value*	p-value *	0.0141 ‡	<0.0001 ‡	0.0001 ‡	<0.0001 ‡	<0.0001 ‡

[a] p-value for comparison of each dose against placebo; p-values were adjusted by the method of Hochberg
† P1 < 0.0412
* overall p-value obtained from model: Y=TMT INV (Y=outcome variable; TMT=treatment effect; INV=investigator effect)
‡ p < 0.05
** CLIMARA 60 (providing controlled delivery of 0.060 mg estradiol-17β per day) is not approved for sale in Canada.

Study ME-93063[38] was performed to compare the effect of treatment with CLIMARA 50 and CLIMARA 100 patches, and placebo, on the bone mineral density of hysterectomized, post-menopausal women.

Conclusion: Of the 141 subjects randomized, 47 withdrew from the study prematurely (19 of 47 in the CLIMARA 50 group, 13 of 46 in the CLIMARA 100 group, 15 of 48 in the placebo group). Both CLIMARA 50 and CLIMARA 100 showed good efficacy in increasing bone mineral density and menopausal symptom control.

Table 11 – Study ME-93063: efficacy results

An increase in bone mineral density at the hip (trochanteric region, Ward's triangle, femoral neck) and spine (L2-L4)				
Treatment Group	**48 weeks**		**96 weeks**	
	Mean (% change)	**95% C.I.**	**Mean (% change)**	**95% C.I.**
Ward's Triangle				
CLIMARA 100	+1.84	-0.89, +4.57	+4.88*	+2.09, +7.68
CLIMARA 50	+3.70*	+1.80, +5.60	+7.74*	+5.11, +10.37
placebo	-1.43	-3.49, +0.63	-3.18	-6.43, +0.07
Trochanteric				
CLIMARA 100	+3.65*	+2.12, +5.19	+7.60*	+5.78, +9.42
CLIMARA 50	+4.67*	+3.35, +6.00	+7.87*	+5.60, +10.15
placebo	-0.18	-1.84, +1.48	-1.14	-2.76, +0.48
Femoral Neck				
CLIMARA 100	+3.29*	+1.61, +4.98	+5.63*	+3.87, +7.38
CLIMARA 50	+3.57*	+2.35, +4.79	+5.73*	+4.25, +7.21
placebo	0.00	-1.39, +1.38	-1.55	-4.12, +1.03
Spine L2-L4				
CLIMARA 100	+5.60*	+4.19, +7.02	+8.66*	+7.15, +10.18
CLIMARA 50	+4.09*	+2.55, +5.63	+7.25*	+5.74, +8.76
placebo	+0.64	+0.50, +1.77	+0.38	-1.11, +1.86

Note: positive values indicated an increase in bone density
* p-value > 0.05 vs. placebo

DETAILED PHARMACOLOGY

Pharmacodynamics

Guinea pig sensitization studies were conducted with placebo and CLIMARA (estradiol hemihydrate transdermal system). No positive responses were observed during the challenge phase of these studies.

In humans, the potential for skin irritation was assessed in three clinical trials. An open-label 21-day cumulative irritation study compared CLIMARA with ESTRADERM® (estradiol hemihydrate transdermal system), Micropore® (an inert tape) and placebo in 23 postmenopausal women. Both Micropore and ESTRADERM are products which are available in Canada. Results indicated that the irritation potential of CLIMARA was minimal, with ESTRADERM being slightly more irritating than CLIMARA.

Another study conducted in 99 postmenopausal women showed a similar incidence of skin irritation between CLIMARA and ESTRADERM. Some degree of irritation was noted at some time point during the 3 week study in 75% and 70% of subjects wearing CLIMARA and ESTRADERM, respectively. By the end of the third week of the study, clinically

significant irritation (defined as mild erythema with symptoms of itching, burning or stinging or a moderate to severe erythema with or without symptoms) was observed in 9% of CLIMARA subjects versus 11% of ESTRADERM subjects.

The third study compared the degree of irritation caused by CLIMARA with that of ESTRADERM in a total of 482 (241 per treatment) postmenopausal women, over a 4 week period. The overall incidence of irritation was high for both systems: 87% in the CLIMARA group and 77% in the ESTRADERM group. At the week 4 evaluation (primary endpoint), there was no difference between the two treatment groups (14.1% in the CLIMARA group and 14.8% in the ESTRADERM group).

A sensitization study was conducted in 102 postmenopausal women. Most subjects had no visible irritation to either active or placebo CLIMARA, during initial testing or during the challenge phase. Only 2 subjects showed some irritation following challenge; they received a second challenge, after which they showed no irritation. It was concluded that CLIMARA exhibited minimal potential for contact sensitization.

Pharmacokinetics

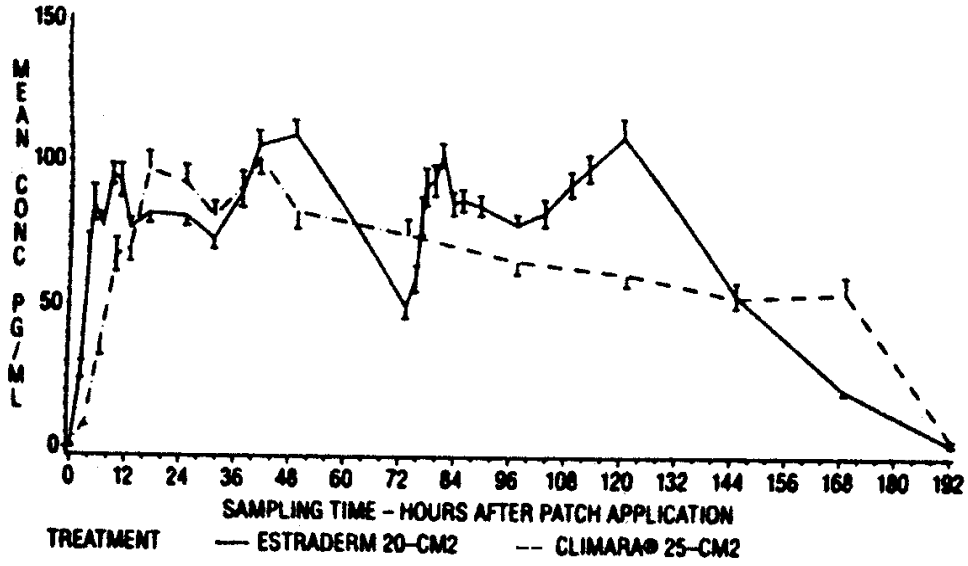
The CLIMARA 25, CLIMARA 50, CLIMARA 75 and CLIMARA 100 systems deliver 0.025 mg, 0.05 mg, 0.075 mg and 0.1 mg of estradiol per day, respectively, into the systemic circulation. In a 3-week multiple-application study in 24 postmenopausal women, the CLIMARA 100 system produced average peak estradiol concentrations of approximately 100 pg/mL. Trough values at the end of each wear interval were approximately 35 pg/mL. Nearly identical serum curves were seen each week, indicating little or no accumulation of estradiol in the body. Serum estrone peak and trough levels were 60 and 40 pg/mL, respectively. Serum concentrations of estradiol and estrone returned to preapplication levels within 6 to 24 hours after removal of the last system (to less than 17 pg/mL of estradiol and 30 pg/mL estrone).

Linear pharmacokinetics have been demonstrated for CLIMARA. In a 1-week application study in 54 postmenopausal women, the CLIMARA 100 system produced estradiol serum profiles and pharmacokinetic parameters that were twice as high as the CLIMARA 50 system. Statistical analyses confirmed the 2:1 dose proportionality.

On average, CLIMARA 100 maintained mean steady-state serum estradiol levels of approximately 70 pg/mL and CLIMARA 50 maintained mean steady-state serum estradiol levels of approximately 35 pg/mL.

Two studies compared a single, 1-week application of CLIMARA with consecutive 3-day and 4-day applications of ESTRADERM. CLIMARA 100 (25 cm^2) was compared with the ESTRADERM 20 cm^2 system (see Figure 1) and CLIMARA 50 (12.5 cm^2) was compared to the ESTRADERM 10 cm^2 system. For a 1-week treatment period, both sizes of the CLIMARA systems maintained significantly lower peak and mean steady-state levels than the comparator system; however, towards the end of each treatment period, CLIMARA maintained similar (day 6) or higher (day 7) serum estradiol levels than ESTRADERM. As a result, the peak-to-end of application interval trough level fluctuations were 3- to 4-times less with CLIMARA.

Figure 1 - Mean Serum Estradiol Levels For a One-Week Application of the CLIMARA 100 (25 cm^2) and Consecutive Three-Day and Four-Day Applications of the ESTRADERM System (20cm^2)



TOXICOLOGY

Animal Toxicology

The toxicity of CLIMARA (estradiol hemihydrate transdermal system) was assessed in rabbits and guinea pigs. In standard primary skin irritation tests performed in albino rabbits, irritation scores for both intact and abraded skin sites, and for the active and placebo systems, were similar. CLIMARA was rated to be a slight irritant due to the minimal erythema observed following removal of the systems; all irritation resolved by 48 hours following system removal.

A cumulative dermal irritation study, also conducted in rabbits, compared the irritation potential of CLIMARA, ESTRADERM and placebo. ESTRADERM is a product which is available in Canada. Irritation produced by CLIMARA and placebo systems were similar for both intact and abraded skin sites, and generally resolved within 48 hours following removal of the systems. ESTRADERM was shown to be less irritating than CLIMARA, but this difference was attributed to the poorer adhesion of ESTRADERM, which resulted in a less complete occlusion of the skin test sites.

Special Tolerance Studies in Humans

Cytotoxicity studies conducted with CLIMARA yielded results within the acceptable range based on historical data from other adhesive systems such as surgical tape.

The adhesive system for the CLIMARA system is a copolymer consisting primarily of isooctyl acrylate (IOA) with a smaller amount of vinyl acetate (VoAc) and an even lesser amount of acrylamide (ACM). Both IOA and VoAc are not mutagenic nor carcinogenic and low levels of any residual monomer in the adhesive would not pose any safety risk to patients wearing the CLIMARA system. However, toxicity testing of ACM has demonstrated mutagenic and carcinogenic potential. Carcinogenic effects were not found in a study of workers exposed to environmental ACM in the workplace. Since the Climara 100 (25 cm^2) system can contain a very low level of residual ACM monomer (i.e., 9.6 µg) a risk assessment was performed. It was demonstrated that exposure of ACM from CLIMARA was less than ambient environmental lifetime ACM exposure from drinking water.

Long-term continuous administration of natural and synthetic estrogens in certain animal species increase the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver (See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

ESTRADERM® is a registered trademark of NOVARTIS.

Micropore® is a registered trademark of 3M.

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PART III: CONSUMER INFORMATION

Pr CLIMARA ® 25
PrCLIMARA® 50
PrCLIMARA® 75
PrCLIMARA® 100

estradiol hemihydrate transdermal system

This leaflet is Part III of a three-part "Product Monograph" published when CLIMARA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CLIMARA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

CLIMARA is approved for use in the following situations:

- To provide relief from the symptoms of menopause

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 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 flushes"). Hot flushes 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 can occur in and around the vagina (causing itching, burning, dryness, painful intercourse) and urethra (causing difficulty or burning during urination and frequent voiding). These changes may improve with estrogen therapy.

CLIMARA 50, CLIMARA 75 and CLIMARA 100 are approved for use in the following situations:

- To help prevent you from developing osteoporosis (thin weak bones)

After menopause, all women start to lose calcium from their bones at an accelerated rate due to a decrease in the amount of estrogen produced by the body. In time, this may cause a thinning of the bones called osteoporosis which makes them weaker and more likely to break, often leading to fractures of the vertebrae, hip and wrist bones. Taking estrogens after menopause may slow down bone loss and may prevent bones from breaking.

CLIMARA is to be considered in light of other available therapies for the prevention of postmenopausal osteoporosis. Discuss adequate diet, calcium and vitamin D intake, cessation of smoking as well as regular physical weight bearing exercise with your doctor or pharmacist in addition to the administration of CLIMARA.

Those women who are likely to develop osteoporosis include those with a strong family history of osteoporosis or bone fractures in older ages, and those who are white, thin, smoke cigarettes, and do not exercise.

Women who have an early menopause or undergo removal of their ovaries at an early age are at greater risk of developing osteoporosis at an earlier age.

In women with intact uteri, CLIMARA should always be taken with a progestin. If your uterus has been surgically removed, endometrial hyperplasia cannot occur and cyclical administration of a progestin is not necessary.

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

Uses of Progestins:

The estradiol delivered by CLIMARA may not only relieve 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 intact uteri, 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), which increases the risk of endometrial cancer (cancer of the lining of the uterus). The risk of endometrial hyperplasia is reduced if a progestin medication is given regularly for a certain number of days with your estrogen replacement therapy.

CLIMARA 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 about whether you still need treatment with HRT.

What it does:

CLIMARA is a medicated patch that contains the hormone estrogen (estradiol), the same hormone that is produced naturally in the body. When you place this patch on your skin, the hormone is transferred to your body through your skin.

When it should not be used:

- You should not take CLIMARA if you:
- are pregnant or if you are breastfeeding
- have active liver disease, or have or have ever had a liver tumour (benign or malignant)
- have a personal history of certain types of cancer, such as endometrial cancer (cancer of the lining of the uterus). If you have or had cancer, talk with your doctor about whether you should take CLIMARA
- have known, suspected or past history of breast cancer. If you have or had cancer, talk with your doctor about whether you should take CLIMARA
- 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
- 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
- have had an allergic or unusual reaction to estrogen or any component of CLIMARA

What the medicinal ingredient is:

estradiol hemihydrate

What the nonmedicinal ingredients are:

acrylate copolymer (consisting of isooctyl acrylate, acrylamide, vinyl acetate copolymer), ethyl oleate, glyceryl monolaurate, isopropyl myristate

What dosage forms it comes in:

The CLIMARA patch is available in four sizes: CLIMARA 25 (containing 2.0 mg of estradiol), CLIMARA 50 (containing 3.8 mg of estradiol), CLIMARA 75 (containing 5.7 mg of estradiol) and CLIMARA 100 (containing 7.6 mg of estradiol).

Each box of CLIMARA contains 4 patches.

WARNINGS AND PRECAUTIONS

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, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large 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.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.

  Estrogens with or without progestins should be used at **the lowest effective dose** and for **the shortest period of time** possible. Regular medical follow-up is advised.

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.

The results of the WHI trial indicated no difference in the risk of breast cancer in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

Estrogens 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.

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).

If you still have your uterus you should take a progestin medication (another hormone drug) regularly for a certain number of days 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.

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.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

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.

Tumours on the Liver

Benign tumours on the liver have been associated with the use of combined estrogen and progestin oral contraceptives. Although benign and rare, these tumours may rupture and cause death from bleeding in the

abdominal cavity. Such tumours have not yet been reported in association with other estrogen or progestin preparations, but they should be considered if abdominal pain and tenderness occurs, or if there is a large abdominal mass, or if sudden and significant drop in blood pressure occurs as a result of the bleeding. Liver cancer has also been reported in women taking estrogen-containing oral contraceptives, however, it is not known if this occurred as a result of taking these drugs.

BEFORE you use CLIMARA talk to your doctor or pharmacist if you:

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have or have had chloasma (yellow-brown patches on the skin);
- have inherited deafness (otosclerosis)
- have systemic lupus erythematosus (SLE; a chronic inflammatory disease)
- have or have had chorea minor (illness with unusual movements)
- have been told that you have a condition called hereditary angioedema or if you have episodes of rapid swelling of hands, feet, face, lips, eyes, tongue, throat (airway blockage), or digestive tract
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- are undergoing surgery or need long bed rest
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have been diagnosed with high prolactin levels or prolactinoma
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- are breastfeeding
- have had a hysterectomy (surgical removal of the uterus)
- smoke
- have a history of depression

Driving or Using Machines

The effects of CLIMARA on the ability to drive or to use machines have not been studied.

INTERACTIONS WITH THIS MEDICATION

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 and CLIMARA may interfere with the effects of other medicines.

Drugs that may interact with CLIMARA 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, ritonavir-boosted protease inhibitors, boceprevir, telaprevir, nevirapine)
- barbiturates, 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.

PROPER USE OF THIS MEDICATION

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

Usual dose:

The CLIMARA patch contains estradiol. When applied to the skin as directed below, CLIMARA releases estradiol which passes through the skin into the bloodstream.

Each CLIMARA 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.

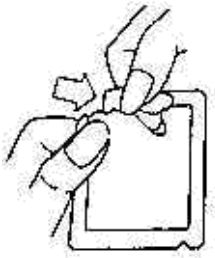
The CLIMARA patch should be applied once a week and worn continually for all 7 days. Remove the patch and apply a new one after 7 days. Only one CLIMARA patch should be worn at any one time during each 7-day time interval.

If you use the CLIMARA patch, and you still have your uterus, you should take a progestin medication (another hormone drug) regularly for a certain number of days to reduce the risk of endometrial hyperplasia or endometrial cancer.

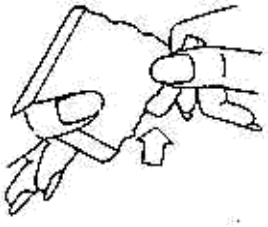
How to apply CLIMARA

Never cut the pouch with scissors – you might damage the patch inside.

To open the pouch, hold it vertically with the name CLIMARA facing you. Tear the pouch at the notch provided at the top of the left-hand corner, tearing from left to right.

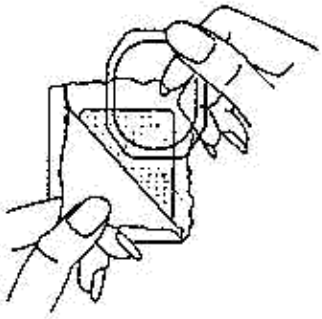


Next, open the right side of the pouch using the notch at the bottom of the right-hand corner and tear from bottom to top.



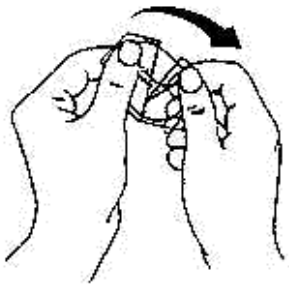
There is a silver-foil sticker securely attached to the inside of the pouch. This contains a moisture protectant. Do not remove it. The foil sticker does not contain medication. Discard it with the empty pouch.

Carefully remove the patch.



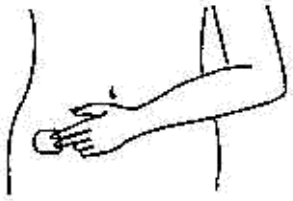
A diagonally-split protective plastic backing covers the adhesive side of the patch and must be removed before applying it. The patch itself is oval and translucent.

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



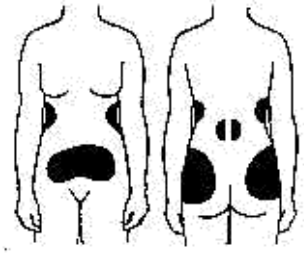
Using the other half of the backing as a handle, apply the sticky side of the patch to the skin. Peel away the other side of the backing and press the entire patch firmly to the skin (see Where To Apply CLIMARA, below). Discard the protective backing.

Apply firm pressure around the edges for about 10 seconds to make sure there are no air bubbles under the patch.



Where to apply CLIMARA

Apply the adhesive side of the patch to a clean dry area of the skin on the trunk of your body or buttocks. **Do not apply CLIMARA to your breasts due to potentially harmful effects on the breast tissue.** Avoid the waistline, since tight clothing may rub and remove the patch. The sites of application 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, above). Press the patch firmly in place with the fingers for about 10 seconds, making sure there is good contact, especially around the edges.



CLIMARA 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 against the patch.

When to apply CLIMARA

CLIMARA should be changed once a week. When changing the patch, remove the used CLIMARA patch and discard it. 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 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 will not affect the patch. In the unlikely event that a patch should fall off, a new patch should be applied for the remainder of the 7-day dosing interval.

Helpful Hints

If the patch falls off, such as in a very hot bath or shower, dry your skin completely and then apply a new patch (to a new area of skin) 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

Patches may stick better 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 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 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 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

Overdosage of estrogen may cause nausea, breast discomfort, bloating or vaginal bleeding in women.

If you think that you have taken an overdose of CLIMARA, remove the patch.

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects generally do not require medical attention, and will usually go away as your body adjusts to CLIMARA:

Common: breast pain, breast tenderness, bloating, dizziness, localized darkening of the skin, mood swings, redness or mild irritation under or around the patch, changes in genital bleeding pattern (including breakthrough bleeding and spotting), headache, weight gain

Uncommon: muscle cramps, breast enlargement,

If you think you are reacting poorly to CLIMARA or are having other problems, please tell your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom/ possible side effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abdominal pain, nausea or vomiting		✓	
	Changes in body weight	✓		
	Heavy periods	✓		
	Migraine headaches	✓		
	Persistent skin irritation	✓		
	Retention of fluid	✓		
	Unexpected vaginal bleeding		✓	
Uncommon	Breast lump		✓	
	Change in speech			✓
	Change in vision		✓	
	Crushing chest pain or chest heaviness			✓
Uncommon	Easy bruising, excessive nose bleeds, excessive heavy periods		✓	
	First migraine headache		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom/ possible side effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Fluid retention or bloating persisting for more than 6 weeks		✓	
	High blood pressure		✓	
	Pain or swelling in the leg			✓
	Persistent sad mood			✓
	Rapid pulse or dizziness		✓	
	Sharp pain in the chest, coughing blood or sudden shortness of breath			✓
Uncommon	Skin redness, warmth, swelling, tenderness, pain or hardening of tissue around a vein		✓	
	Sudden partial or complete loss of vision			✓
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			✓
	Vomiting		✓	
	Yellowing of the skin or eyes (jaundice)			✓

This is not a complete list of side effects. For any unexpected effects while taking CLIMARA, contact your doctor or pharmacist.

HOW TO STORE IT

Keep CLIMARA in its sealed pouch until you are ready to use it. Store at 15 - 30°C (room temperature). Do not freeze. Apply CLIMARA immediately upon removal from the protective pouch. CLIMARA should be kept out of the reach of children before and after use.

REPORTING SUSPECTED SIDE EFFECTS

Canada Vigilance Program

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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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