

REGISTERED PACKAGE INSERT

SCHEDULING STATUS

S4

PROPRIETARY NAMES AND DOSAGE FORMS

CLIMARA 25
CLIMARA 50
CLIMARA 75
CLIMARA 100

Estradiol transdermal systems

COMPOSITION

- Climara 25: 6,5 cm² patch containing 2,04 mg of estradiol hemihydrate (corresponding to estradiol 1,97 mg).
- Climara 50: 12,5 cm² patch containing 3,9 mg of estradiol hemihydrate (corresponding to estradiol 3,8 mg).
- Climara 75: 18,75 cm² patch containing 5,9 mg of estradiol hemihydrate (corresponding to estradiol 5,7 mg).
- Climara 100: 25,0 cm² patch containing 7,8 mg of estradiol hemihydrate (corresponding to estradiol 7,6 mg).

PHARMACOLOGICAL CLASSIFICATION

A. 21.8.1 Estrogens.

PHARMACOLOGICAL ACTION

Estrogens are largely responsible for development and maintenance of the female reproductive and secondary sexual characteristics. Estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites estrone and estriol at receptor level. Circulating estrogens modulate the pituitary secretion of gonadotrophins, luteinising hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism.

After dermal application of Climara, estradiol is absorbed through the skin. Nominal average estradiol absorption rates of 25, 50, 75 and 100 µg/day were calculated for Climara 25, Climara 50, Climara 75 and Climara 100, respectively.

During a once-a-week application regimen of Climara patches, smooth and consistent estradiol and estrone serum level profiles within the desired range are achieved. The estradiol serum level profile is directly proportional to the area of the patch. Mean steady state estradiol serum levels are approximately 18 pg/ml (6,5 cm² patch), 35 pg/ml (12,5 cm² patch), 53 pg/ml (18,75 cm² patch) and 70 pg/ml (25 cm² patch).

Observational studies in the Women's Health Initiative trial on conjugated equine estrogens plus medroxyprogesterone acetate suggest a reduction of colon cancer morbidity in postmenopausal women taking hormone replacement therapy. In the Women's Health Initiative trial on conjugated equine

estrogen mono therapy a risk reduction was not observed. It is unknown whether these findings also extend to other hormone replacement therapy products.

INDICATIONS**Climara 25, Climara 50, Climara 75, Climara 100**

Estrogen replacement therapy for patients with symptoms due to natural menopause or surgically induced menopause (only if due to noncarcinomatous diseases) eg vasomotor symptoms (hot flushes).

Climara 50, Climara 75, Climara 100

To reduce the risk of postmenopausal osteoporosis.

CONTRA-INDICATIONS

Hormone replacement therapy should not be started in the presence of any of the conditions listed below. Should any of the conditions appear during hormone replacement therapy use, the product should be stopped immediately.

- Pregnancy and lactation.
- Undiagnosed abnormal genital bleeding.
- Known or suspected cancer of the breast.
- Known or suspected premalignant conditions or malignancies, if sex steroid-influenced.
- Presence or history of liver tumours (benign or malignant).
- Acute arterial thromboembolism (eg myocardial infarction, stroke).
- Active deep venous thrombosis, thromboembolic disorders, or a documented history of these conditions.
- Known hypersensitivity of any of the components of Climara patches.

WARNINGS**Medical examination/consultation**

A complete medical history should be taken and a physical examination should be conducted prior to the initiation or reinstatement of hormone replacement therapy, guided by the "Contra-indications" and "Warnings" and should be repeated periodically. The frequency and nature of these examinations should be based on established practice guidelines and be adapted to the individual woman, but should generally include pelvic organs, including routine cervical cytology, abdomen, breasts and blood pressure.

Venous thromboembolism

Both randomised-controlled and epidemiological studies have suggested an increased relative risk of developing venous thromboembolism, ie deep venous thrombosis or pulmonary embolism. Benefit/risk should therefore be carefully weighed in consultation with the patient when prescribing hormone replacement therapy to women with a risk factor for venous thromboembolism.

Generally recognised risk factors for venous thromboembolism include a personal history, a family history (the occurrence of venous thromboembolism in a direct relative at a relatively early age may indicate genetic disposition) and severe obesity. The risk of venous thromboembolism also increases with age. There is no consensus about the possible role of varicose veins in venous thromboembolism.

The risk of venous thromboembolism may be temporarily increased with prolonged immobilisation, major elective or post-traumatic surgery, or major trauma. Depending on the nature of the event and the duration of the immobilisation, consideration should be given to a temporary discontinuation of hormone replacement therapy.

Treatment should be stopped at once if there are symptoms of a thrombotic event or suspicion thereof.

Arterial thromboembolism

Two large clinical trials with continuous combined conjugated equine estrogens and medroxyprogesterone acetate showed a possible increased risk of coronary heart disease in the first year of use and no benefit thereafter. One large clinical trial with conjugated equine estrogens alone showed a potential reduction of coronary heart disease rates in women aged 50 to 59 and no overall benefit in the total study population. As a secondary outcome in two large clinical trials with conjugated equine estrogens alone or combined with medroxyprogesterone acetate, a 30 to 40% increased risk of stroke was found. It is uncertain whether these findings also extend to other hormone replacement therapy products or non-oral routes of administration.

Endometrial cancer

Prolonged exposure to unopposed estrogens increases the risk of development of endometrial hyperplasia or carcinoma. Studies have suggested that the appropriate addition of progestogens to the regimen eliminates this increase.

Breast cancer

Clinical and observational studies have reported an increased risk of having breast cancer diagnosed in women taking hormone replacement therapy for several years. The findings may be due to an earlier diagnosis, growth promoting effects on pre-existing tumours, or a combination of both.

Estimates for the overall relative risks of breast cancer diagnosis given in more than 50 epidemiological studies ranged in the majority of the studies between 1 and 2.

The relative risk increases with duration of treatment and may be lower or possibly neutral with estrogen-only products.

Two large randomised trials with conjugated equine estrogens alone or continuously combined with medroxyprogesterone acetate showed risk estimates of 0,77 (95% CI: 0,59-1,01) or 1,25 (95% CI: 1,01-1,54) after approximately 6 years of hormone replacement therapy use. It is unknown whether the increased risk also extends to other hormone replacement products.

Similar increases in breast cancer diagnosis are observed e.g. with delay of natural menopause, alcohol intake, or adiposity.

The excess risk disappears within a few years after stopping hormone replacement therapy.

Most studies have reported that tumours diagnosed in current or recent users of hormone replacement therapy tend to be better differentiated than those found in non-users. Data regarding spread outside the breast are not conclusive.

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

Ovarian cancer

An epidemiological study found a slightly increased risk in ovarian cancer for women on long-term (more than 10 years) estrogen replacement therapy, while a meta-analysis of 15 studies did not find an increased risk for women on estrogen replacement therapy. Therefore the influence of estrogen replacement therapy on ovarian cancer is not clear.

Liver tumours

In rare cases benign and malignant liver tumours may lead to life-threatening intraabdominal haemorrhage after the use of sex steroid containing preparations. If severe upper abdominal complaints, liver enlargement or signs of intraabdominal haemorrhage occur, a liver tumour should be included in the differential-diagnostic considerations.

Gallbladder disease

Estrogens are known to increase the lithogenicity of the bile. Some women are predisposed to gallbladder disease during estrogen therapy.

Dementia

There is limited evidence from clinical studies with conjugated equine estrogen-containing preparations that hormonal treatment may increase the risk of probable dementia if initiated in women aged 65 or older. The risk may be decreased if treatment is initiated in the early menopause, as observed in other studies. It is unknown whether these findings also extend to other hormone replacement therapy products.

Other conditions

Treatment should be stopped at once if migrainous or frequent and unusually severe headaches occur for the first time, or if there are other symptoms that are possible premonitory signs of cerebrovascular occlusion.

If there is, repeatedly, persistent skin irritation (eg persistent erythema or pruritus at the application site) despite application sites being changed according to directions, consideration should be given to discontinuing transdermal treatment.

A generalised association between hormone replacement therapy use and development of clinical hypertension has not been established. Small increases in blood pressure have been reported in women taking hormone replacement therapy; clinically relevant increases are rare. However, if in individual cases a sustained clinically significant hypertension develops during the use of hormone replacement therapy, then withdrawing the hormone replacement therapy may be considered.

Sex steroids may be poorly metabolised in patients with impaired liver function. Although transdermally administered hormone replacement therapy avoids first-pass hepatic metabolism, hormone replacement therapy should still be administered with caution in such patients.

Recurrence of cholestatic jaundice or cholestatic pruritus which occurred first during pregnancy or previous use of sex steroids necessitates the immediate discontinuation of hormone replacement therapy.

Certain patients may develop undesirable manifestations of estrogen stimulation under hormone replacement therapy such as abnormal uterine bleeding. Frequent or persistent abnormal uterine bleeding during treatment is an indication for endometrial assessment.

Uterine myomas may increase in size under the influence of estrogens. If this is observed, treatment should be discontinued.

Should endometriosis be reactivated under treatment, discontinuation of therapy is recommended.

Should there be a suspicion of a prolactinoma, this should be ruled out before starting treatment.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking hormone replacement therapy.

The following conditions have been reported to occur or deteriorate with hormone replacement use. Although the evidence of an association with hormone replacement therapy use is inconclusive, women with these conditions and treated with hormone replacement therapy should be carefully monitored.

- Epilepsy
- Benign breast disease
- Asthma
- Migraine

- Porphyria
- Otosclerosis
- Systemic lupus erythematosus
- Chorea minor

INTERACTIONS

Hormonal contraception should be stopped when hormone replacement therapy is started and the patient should be advised to take non-hormonal contraceptive precautions, if required.

Interaction with drugs

Long-term treatment with hepatic enzyme-inducing drugs (eg several anticonvulsants and antimicrobials) can increase the clearance of sex hormones and may reduce clinical efficacy. Such hepatic enzyme-inducing properties have been established for hydantoins, barbiturates, primidone, carbamazepine, and rifampicin and are also suspected for oxcarbazepine, topiramate, felbamate and griseofulvin. Maximal enzyme induction is generally not seen before 2 to 3 weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Interaction with alcohol

Acute alcohol ingestion during use of hormone replacement therapy may lead to elevations in circulating estradiol levels.

Interaction with laboratory tests

The use of sex steroids may influence biochemical parameters of eg liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins such as corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism, and parameters of coagulation and fibrinolysis.

PREGNANCY AND LACTATION

Hormone replacement therapy is not indicated for use during pregnancy or lactation. If pregnancy occurs during medication with Climara, treatment should be withdrawn immediately.

Extensive epidemiological studies with steroid hormones used for contraception and hormone replacement therapy have revealed neither an increased risk of birth defects in children born to women who used such hormones prior to pregnancy, nor a teratogenic effect when they were taken inadvertently during early pregnancy.

Small amounts of sex hormones may be excreted in human milk.

DOSAGE AND DIRECTIONS FOR USE

Treatment should be initiated with the lowest Climara patch dose, applied to the skin on the lower trunk once weekly. If it is considered necessary, a higher dose should be used.

Once treatment has been initiated, the lowest effective dose necessary for the relief of symptoms should be established.

The treatment can be given without interruption or it can be interrupted for 1 week after every 3 weeks.

For risk reduction of osteoporosis: Treatment with Climara 50, Climara 75 or Climara 100 patches to reduce the risk of postmenopausal bone loss should be initiated as soon as possible after the menopause. Treatment should be based on individual considerations.

Unopposed estrogen therapy should not be used unless the patient has had a hysterectomy. In all other cases the appropriate dose of a progestogen should normally be administered for 10 to 12 days in every month to avoid endometrial hyperplasia and the consequent increased risk of endometrial carcinoma.

If a continuous treatment regimen has been chosen, the administration of a progestogen may be initiated at an arbitrarily selected time (eg at the beginning or at the end of a month) and should be repeated at regular intervals of about 4 weeks.

If a cyclical (3 week) treatment regimen has been chosen, the progestogen should be administered during the last 10 to 12 days of the cycle.

A menstruation-like bleeding normally occurs 2 to 3 days after the end of the period of progestogen administration.

Following removal of the protective liner the adhesive side of Climara patches should be placed on a clean, dry area of the skin of the trunk. Climara patches should not be applied to the breasts. The sites of application should be rotated, with an interval of at least one week between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided since tight clothing may rub the patch off. The patch should be applied immediately after opening the pouch and removing the protective liner. The patch should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges.

The patch should be changed once weekly.

If the patch is applied correctly, the patient can bath or shower as usual. The patch might, however, become detached from the skin in very hot bath water or in the sauna.

In the event that a patch falls off, a new patch should be applied for the remainder of the 7 day dosing interval.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Serious undesirable effects associated with the use of hormone replacement therapy are also mentioned under "Warnings".

The table below attributes frequencies to the undesirable effects of Climara. These frequencies are based on clinical trial data. The most commonly reported adverse reactions with Climara during clinical trials were skin irritation at the application site and breast pain (> 10%). Symptoms at the application site are typically mild and may include erythema, itching, a stinging sensation or vesicle formation. A summary of the most common adverse reactions with Climara is provided within the tables below:

System organ classification (SOC)	Common ($\geq 1/100$, < 1/10)	Uncommon ($\geq 1/1000$, < 1/100)
Gastrointestinal disorders	Abdominal pain, bloating, nausea.	
General disorders and administration site conditions	Oedema.	
Investigations	Changes in body weight.	
Musculoskeletal and connective tissue disorders		Muscle cramps.
Nervous system disorders	Headache, dizziness.	Migraine.
Reproductive system and breast disorders	Breast tenderness, changes in uterine bleeding pattern (including breakthrough bleeding and spotting).	Breast enlargement.

Other side-effects that have been reported in users of estrogen replacement therapy but for which the association to Climara has neither been confirmed nor refuted are:

	Adverse event
Congenital, familial and genetic disorders	Worsening of porphyria.
Gastrointestinal disorders	Vomiting.
Hepatobiliary disorders	Cholestatic jaundice.
Psychiatric disorders	Changes in libido.
Reproductive system and breast disorders	Increase in size of uterine leiomyomas, changes in the amount of cervical secretion.
Skin and subcutaneous tissue disorders	Chloasma or melasma which may persist after the drug is discontinued, allergic contact dermatitis, post-inflammatory pruritus, generalised exanthema.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage is unlikely with this type of application. Overdosage may cause nausea and vomiting and withdrawal bleeding may occur in some women. There is no specific antidote. Treatment should be symptomatic and the patch(es) should be removed.

IDENTIFICATION

A protective pouch containing an oval Climara 25 patch (approximately 3,2 x 2,4 cm) with a surface area of 6,5 cm², an oval Climara 50 patch (approximately 4,5 x 3,3 cm) with a surface area of 12,5 cm², an oval Climara 75 patch (approximately 5,5 x 4,1 cm) with a surface area of 18,75 cm², or an oval Climara 100 patch (approximately 6,3 x 4,7 cm) with a surface area of 25 cm². The patches comprise two layers: an acrylate adhesive matrix containing estradiol on a translucent (see-through) polyethylene film. A clear protective liner of release-coated polyester film is attached to the adhesive surface and must be removed prior to use. The protective pouch contains a desiccant.

PRESENTATION

Packs containing 4 patches.
Packs containing 12 patches.

STORAGE INSTRUCTIONS

Store below 30°C. For shelf-life, refer to imprint on the pack. Keep out of reach of children. Do not store unpouched. Apply immediately upon removal from the protective pouch.

REGISTRATION NUMBERS

Climara 25 : 37/21.8.1/0214
Climara 50 : 29/21.8.1/0610
Climara 75 : 35/21.8.1/0032
Climara 100 : 29/21.8.1/0611

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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REGISTERED PACKAGE INSERT

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