

CLIMARA[®] -50, -100

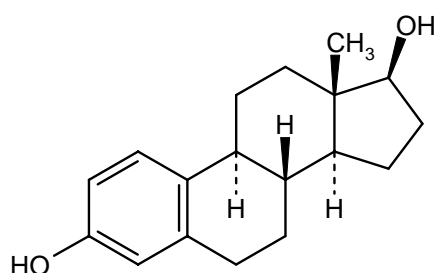
Oestradiol transdermal delivery systems

Presentation

CLIMARA is a transdermal delivery system containing oestradiol as the active ingredient. Oestradiol is estra-1,3,5(10)-triene-3,17 β -diol, the major oestrogenic hormone produced by the human ovary. The remaining components of the system are pharmacologically inactive.

The CAS Registry number for oestradiol is 50-28-2

Structural Formula



The CLIMARA transdermal delivery system is a transparent oval patch containing oestradiol in an acrylate adhesive matrix. Two strengths of CLIMARA are available 50 and 100.

	CLIMARA 50	CLIMARA 100
Oestradiol content:	3.8 mg (equivalent to 3.9 mg oestradiol hemihydrate)	7.6 mg (equivalent to 7.8 mg oestradiol hemihydrate)
Size (release area):	12.5 cm ²	25 cm ²
Nominal daily <i>in vivo</i> release of oestradiol	50 μ g	100 μ g

When applied to intact skin, the transdermal delivery from CLIMARA patches is maintained over 7 days. Transdermal delivery of oestradiol overcomes the problems of its short half-life, seen when oestradiol is given orally, due to extensive first pass metabolism.

The CLIMARA transdermal delivery system is comprised of two layers.

1. A backing layer of translucent polyethylene film
2. Oestradiol in an adhesive matrix.

A protective liner is attached to the adhesive surface. This must be removed prior to applying the patch to the skin.

The excipients of the CLIMARA transdermal delivery system include acrylate copolymer adhesive, fatty acid esters and polyethylene backing. CLIMARA patches do not contain alcohol.

Uses

Actions

Pharmacodynamics

CLIMARA provides systemic oestrogen replacement therapy by releasing oestradiol. Oestradiol is the major oestrogenic hormone secreted by the human ovary from the menarche to the menopause and is the most potent of the endogenous oestrogens.

Oestrogens are important in the development and maintenance of the female reproductive system and secondary sexual characteristics. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures and changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination. Oestrogens play an important role in various metabolic processes, including the modulation of bone resorption.

Oestrogens exert their metabolic effects by binding to specific receptors in target cells. Oestrogen receptors have been identified in all known oestrogen target organs including the uterus, hypothalamus, pituitary, vagina, urethra, breast, liver and osteoblasts.

There are several forms of naturally occurring oestrogen. Oestradiol is the principal intracellular human oestrogen and is substantially more potent than the others, oestrone or oestriol. The ovarian follicle secretes 70 to 500 micrograms of oestradiol daily, varying with the phase of the menstrual cycle. This is converted primarily to oestrone, and to small amounts of oestriol in the liver. The oestradiol/oestrone ratio during fertile life is greater than 1. However, in postmenopausal women, oestrone is the most abundant circulating oestrogen. After menopause, when the ovaries have ceased to function, oestrone is produced from the aromatisation of androstenedione and only small amounts of oestradiol are produced from metabolic conversion of testosterone and oestrone.

The oestrogen deficiency around and after the menopause produces symptoms such as severe hot flushes, night sweats, insomnia, dyspareunia and progressive atrophy of the urogenital system in many women. These disorders can be largely eliminated by means of oestrogen replacement therapy. There is also an increased risk of bone fractures and osteoporosis, particularly of the vertebral column, hip, and wrist due to the increased loss of bone substance caused by low levels of oestrogen, and cardiovascular

disease. Short-term treatment with oestrogen replacement therapy perimenopausally has been shown to prevent loss of bone density. There is currently no evidence of the minimum duration of oestrogen replacement therapy, which will be effective for younger postmenopausal women in reducing fracture when they reach 75 years of age (the age of greatest fracture risk).

Known risk factors for post-menopausal osteoporosis include early menopause or surgical oophorectomy, prolonged secondary amenorrhoea, prolonged systemic steroid use and a family history of osteoporosis. Women especially at risk are those who are Caucasian, small boned, smokers and live a sedentary lifestyle. The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and Vitamin D intake, and when indicated, pharmacologic therapy. When CLIMARA is used for the short term relief of menopausal symptoms, it will provide a concomitant effect in reducing bone mineral density loss.

Transdermal administration of oestrogen offers many advantages over conventional oral delivery. It avoids the hepatic first-pass effects resulting in a constant serum level which reflects the pre-menopausal physiological serum profile and ratio of oestradiol to oestrone. In plasma, the concentration ratio of oestradiol (E_2) to oestrone (E_1) undergoes a shift from between 1:5 and 1:2 to approximately 1:1, i.e. to values which are recorded before the menopause in women with normally functioning ovaries. Gastrointestinal side effects are avoided also. The skin metabolises oestradiol to a small extent only, thus transdermal administration provides therapeutic serum levels of oestradiol using smaller total doses than oral therapy. Constant delivery of the therapeutic dose is maintained with CLIMARA patches over the 7 day application period. However, therapy is easily discontinued by removal of the patch.

Following the application of transdermal oestradiol for 28 days, no effect has been observed on the concentrations or activity of the blood coagulation factors fibrinopeptide A, high molecular weight fibrinogen and antithrombin III. After this period of 28 days, transdermally administered oestradiol did not induce any change in the concentrations either of circulating renin substrate or of the sex hormone binding, thyroxine binding or cortisol binding globulins. It has been found, however, that after only three weeks administration, transdermally administered oestradiol elicits a dose dependent reduction in urinary excretion of calcium and hydroxyproline.

Independent of the route of administration, oestrogen doses, which are necessary for improvement of menopausal complaints, exert a dose dependent stimulating effect on mitosis and proliferation of the endometrium. Oestrogen monotherapy increases the frequency of endometrial hyperplasia and thus the risk of endometrial cancer. In order to avoid endometrial hyperplasia the sequential administration of a progestogen for 10 - 14 days every 4 weeks is recommended in non-hysterectomised postmenopausal women (see "*Warnings and Precautions: WHI study and Million Women study*")

Hormone replacement therapy (HRT) with an adequate oestrogen dosage reduces bone resorption and retards or halts postmenopausal bone loss. When HRT is discontinued, bone mass declines at a rate comparable to that in the immediate postmenopausal period. There is no evidence that HRT restores bone mass to premenopausal levels.

Pharmacokinetics

Transdermal oestradiol administration aims at achieving smooth, stable, plateau-like oestradiol serum levels similar to those during the early/mid follicular phase of the reproductive life span. Oestradiol serum levels in the range between 30 - 100 pg/mL are necessary for an efficacious transdermal oestrogen replacement therapy. Nominal average *in vivo* absorption rates for CLIMARA 50 and CLIMARA 100 are 50 µg/day and 100 µg/day respectively. In pharmacokinetic studies mean steady state oestradiol levels of 35 pg/mL were obtained after application of the 12.5 cm² CLIMARA 50 patch and 70 pg/mL after application of the 25 cm² CLIMARA 100 patch. No accumulation of either oestradiol or oestrone occurred after multiple one-week applications, with serum levels returning to baseline within 6 hours of patch removal.

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

Two transdermal absorption studies were conducted comparing serum oestradiol level profiles and pharmacokinetic parameters following once-a-week application of CLIMARA patches and twice-a-week applications of another brand of patches (Estraderm). Both patch sizes were examined: In the first study CLIMARA 50 (12.5 cm²) was compared with Estraderm 50 (10 cm²) and in the second study CLIMARA 100 (25 cm²) was compared with Estraderm 100 (20 cm²). With both patch sizes, CLIMARA once-a-week treatments maintained smoother and more stable oestradiol serum level profiles than did the Estraderm twice-a-week patches. C_{max}, AUC and MSS were all significantly higher for the Estraderm patch application, but towards the end of the one-week application interval, both CLIMARA patches maintained similar (144 hours) or higher (168 hours) mean trough serum levels than did the Estraderm patches. The mean peak to end of application interval trough level fluctuations were smaller with CLIMARA than with Estraderm.

The biotransformation and excretion of transdermally administered oestradiol is the same as that of the endogenous hormone. The plasma elimination half-life of oestradiol is approximately one hour. Oestradiol is eliminated from the body with a total serum clearance of approximately 15 - 30 mL/min/kg by biotransformation mainly in the liver but also extrahepatically. Its most important metabolites are oestriol and oestrone and their conjugates (glucuronides and sulphates); these are far less pharmacologically active than oestradiol. The bulk of the conjugates are excreted in the urine. Oestrogen metabolites are also subject to enterohepatic circulation.

Indications

For short-term treatment of complaints associated with the menopause and post-menopause, including signs and symptoms of oestrogen deficiency, whether naturally or surgically induced.

Oestrogen replacement therapy in women with an intact uterus should always be opposed by a progestogen in an adequate dosage regimen to ensure secretory transformation of the endometrium at regular intervals.

Prevention of postmenopausal osteoporosis

Dosage and Administration

Hormone replacement therapy should only be continued for as long as the benefit in alleviation of severe symptoms outweighs the risk for the individual woman. The need for continuing treatment should be reviewed periodically (e.g. at 6-monthly intervals). Treatment should be based on individual considerations (see also "*Warnings and Precautions*").

Initiation of Therapy

Treatment to control postmenopausal symptoms is usually initiated with the CLIMARA 50 patch applied to the skin once weekly. Treatment should begin with the lowest effective dose and be adjusted as necessary until symptoms are controlled. Once treatment is established, the lowest dose necessary for the relief of symptoms should be used. The treatment can be given without interruption or it can be interrupted for one week after every 3 weeks.

For continuous use: A patch should be applied once a week, each used patch being removed after 7 days.

For cyclical use: The patches should be applied weekly for 3 consecutive weeks followed by a seven-day interval, without a patch being applied before the next course.

In women who are not currently taking oral oestrogens, treatment with CLIMARA can be initiated at once. In women who are currently taking oral oestrogens, treatment with CLIMARA can be initiated one week after withdrawal of oral therapy, or sooner if symptoms reappear before the end of the week.

For prevention of osteoporosis: CLIMARA can prevent the accelerated loss of bone density due to oestrogen deficiency and may be used for prevention of postmenopausal bone mineral density loss in the appropriate patient group (see "*Indications*"). The effect is seen only while oestrogen replacement therapy continues and discontinuation may re-establish the natural rate of bone loss. In patients with established osteoporosis and evidence of fractures, therapy should be initiated with CLIMARA 100, to prevent postmenopausal bone loss, as soon as possible after the menopause.

Unopposed oestrogen therapy should not be used unless the patient has had a hysterectomy. In women with an intact uterus, the prolonged use of oestrogens alone in the climacteric can induce hyperplasia of the endometrium and, in this connection, increase the risk of endometrial cancer. This risk can best be minimised by the additional administration of a progestogen, sequentially for at least 10 - 14 days of each calendar month. This generally leads to secretory conversion and shedding of the uterine lining and, as a result, to menstruation-like bleeding after the end of the period of progestogen treatment (see "*Warnings and Precautions*").

If a continuous treatment regimen has been chosen, the administration of a progestogen may be initiated at an arbitrarily selected time (e.g. 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 - 14 days of each 3-week period of oestradiol administration, so that the 4th week of each cycle remains without any treatment.

In either case a withdrawal bleed usually occurs 2 - 3 days after the end of the period of progestogen administration.

Method of Application

Following removal of the protective liner, the adhesive side of the CLIMARA patch should be placed on a clean, dry area of the skin of the trunk (lower abdomen) or buttocks. CLIMARA patches must not be applied on or near 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 patches should not be applied twice in succession to the same site. The area selected should not be oily, damaged or irritated. The waistline should be avoided since tight clothing may rub the patch off. CLIMARA should be applied to skin sites that will be covered by clothes. Application to areas where sitting would dislodge the patch should be avoided. 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. If the patch lifts, pressure should be applied to maintain adhesion.

The patch should be changed once weekly. Only one patch should be worn at any time during the 7-day dosing interval.

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

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

If the patient forgets to replace the patch, this should be done as soon as possible after she notices this. The next patch has to be used after the normal 7-day interval.

Contraindications

Hormone replacement therapy (HRT) should not be started in the presence of any of the conditions listed below. If any of these conditions appear during use of CLIMARA, treatment should be stopped immediately.

- Known allergy to oestradiol or any of the components of the transdermal delivery system
- Severe uncontrolled hypertension
- Pregnancy or lactation
- Suspected or existing tumour of the uterus, breast or ovaries
- Known or suspected premalignant conditions or malignancies, if sex steroid-influenced
- Endometriosis
- Severe disturbances of liver function
- Previous or existing liver tumours, benign or malignant
- Active deep venous thrombosis, thromboembolic disorders, thrombophlebitis, or a recent history of these conditions
- Acute arterial thromboembolism (e.g. angina, myocardial infarction, stroke) or a recent history of these conditions
- Severe diabetes with vascular changes
- Sickle cell anaemia
- Disturbances of lipometabolism
- History of herpes of pregnancy
- Otosclerosis with deterioration during pregnancy
- Jaundice or persistent itching during a previous pregnancy
- Undiagnosed abnormal vaginal bleeding
- Non-hysterectomised women unless on concomitant progestogen therapy

- Hereditary or acquired predisposition to venous thrombosis (e.g. antithrombin III deficiency)

Warnings and Precautions

The benefits and risks of hormone replacement therapy (HRT) must always be carefully weighed, including consideration of the emergence of risks as therapy continues. HRT should only be used for the short term relief of menopausal symptoms. Oestrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with the treatment goals and risks for the individual woman. The risks of HRT should be assumed to be similar for all doses of oestrogens and oestrogen/progestogen combinations. All prospective and current users of HRT should be advised of the risks and benefits of oestrogens and progestogens and the need for treatment should be reviewed on a 6 monthly basis.

Medical Examination/Consultation

A complete medical history should be taken and a physical examination should be conducted prior to the initiation or reinstatement of treatment with CLIMARA, guided by the “*Contraindications*” and “*Warnings and Precautions*” sections, and should be repeated periodically. The frequency and nature of these examinations should be based on established practice guidelines, 6 monthly reviews are generally considered appropriate, and be adapted to the individual woman, but should generally include pelvic organs, including routine cervical cytology, abdomen, breasts and blood pressure. Pregnancy should also be excluded. The need for continued therapy should be reconsidered at each review.

If any of the conditions/risk factors mentioned below are present or deteriorate, an individual risk-benefit analysis should be done before CLIMARA is started or continued.

CLIMARA is not a contraceptive.

Where applicable, contraception should be practised with non-hormonal methods (with the exception of the rhythm and temperature methods). If there is a chance that pregnancy has occurred, tablet taking must be interrupted until it has been ruled out.

Reasons for Immediate Discontinuation

Occurrence for the first time of migrainous headaches or more frequent occurrence of unusually severe headaches, sudden perceptual disorders (e.g. disturbances of vision or hearing) or other symptoms that are possible prodromata of vascular occlusion, first signs of thrombophlebitis or thromboembolic symptoms (for example, unusual pains in or swelling of the legs, stabbing pains on breathing or coughing for no apparent reason), acute arterial thromboembolism (e.g. myocardial infarction, stroke), a feeling of pain

and tightness in the chest, pending operations (six weeks beforehand), immobilisation (for instance, following accidents), onset of jaundice, onset of hepatitis, itching of the whole body, recurrence of cholestatic jaundice or cholestatic pruritis which occurred first during pregnancy or previous use of sex steroids, increase in epileptic seizures, significant rise in blood pressure, pregnancy.

Uterine myomas and pre-existing fibroids may increase in size under the influence of oestrogens. If this is observed, CLIMARA treatment should be discontinued.

Precautions Before Use

Oestrogens with or without progestogens should not be used for the long-term maintenance of general health, including the primary prevention of cardiovascular disease as the risks of long-term treatment with HRT in most circumstances, outweigh the benefits. The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in postmenopausal women during five years of treatment with conjugated equine oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to the placebo (see table below).

The WHI study was designed to investigate the efficacy and safety of long-term HRT in preventing coronary heart disease in healthy postmenopausal women with an intact uterus. A total of 8506 women received HRT and 8102 women received placebo for an average of 5.2 years.

Summary of the incidence of adverse events described in the WHI study

Adverse Event	Relative Risk of HRT vs placebo at 5.2 years (95% CI)	Change in number of adverse events per 10,000 women in one year
Breast cancer	1.26 (1.00 - 1.59)	8 extra
Heart disease	1.29 (1.02 - 1.63)	7 extra
Stroke	1.41 (1.07 - 1.85)	8 extra
Pulmonary embolism	2.13 (1.39 - 3.25)	8 extra
Myocardial infarction	1.32 (1.02 - 1.72)	*
Deep vein thrombosis	2.07 (1.49 - 2.87)	*
Colorectal cancer	0.63 (0.43 - 0.92)	6 fewer
Hip fracture	0.66 (0.45 - 0.98)	5 fewer

* Information not available

Other doses of conjugated oestrogens and medroxyprogesterone acetate and other combinations of oestrogens and progestogens were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, oestrogens and progestogens should be prescribed at the lowest effective doses and for the shortest duration (generally not longer than 3 - 4 years), consistent with the treatment goals and risks for the individual woman, see the “*WHI Study*” section below.

The prolonged use of oestrogens alone in the climacteric can induce hyperplasia of the endometrium and, in this connection, increase the risk of endometrial cancer. This risk can best be minimised by the additional administration of a progestogen, normally for 10 - 14 days per month. This generally leads to secretory conversion and shedding of the uterine lining and, as a result, to menstruation-like bleeding after the end of the period of progestogen treatment (see “*Dosage and Administration*”).

If irregular bleeding occurs repeatedly during the use of CLIMARA, or if the bleeding in the treatment-free weeks is unusually profuse, thorough differential-diagnostic clarification is essential.

If there are repeatedly persistent skin irritations (e.g. persistent erythema or pruritus at the application site) even if the application has been regularly changed as instructed in the directions, one should consider cessation of transdermal treatment.

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

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

The following conditions have been reported to occur or deteriorate with HRT use. Although the evidence of an association with HRT use is inconclusive, close medical supervision is necessary in patients with a history of, or risk factors for, thromboembolic disorders, diabetes, hypertension, varicose veins, asthma, otosclerosis, systemic lupus erythematosus, multiple sclerosis, epilepsy, porphyria, tetany, chorea minor, heart failure, disturbances of kidney or liver function, migraine, endometriosis, chloasma, or a history of chloasma gravidarum. Patients with fibrocystic disease of the breasts and patients with first degree relatives who have had breast cancer also require close supervision and should be instructed in breast self-examination. The same applies to patients with benign tumours of the uterine smooth muscles, since the size of such tumours can increase under oestrogen therapy. It is recommended in long term use that the benefits should be weighed against the risks for each woman.

In women with hereditary angioedema, exogenous oestrogens may induce or exacerbate symptoms of angioedema.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before CLIMARA is started or continued.

Cardiovascular Risk

The WHI study reported increased risks of myocardial infarction and stroke, as well as pulmonary emboli and deep vein thrombosis in postmenopausal women during five years of treatment with oral conjugated equine oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo.

Venous Thromboembolism

Both randomised controlled and epidemiological studies have suggested that HRT may be associated with an increased relative risk of developing venous thromboembolism (VTE), i.e. deep venous thrombosis or pulmonary embolism. CLIMARA is contraindicated in women with a history of or predisposition to thromboembolic disorders.

In a subset of WHI, women in the oral oestrogen plus progestogen group had a two-fold greater rate of VTE, including deep vein thrombosis and pulmonary embolism, compared to women receiving placebo. The rates of VTE were 34 and 16 per 10,000 person years in the treatment and placebo groups respectively. The increase in VTE risk was observed during the first year and persisted.

Risk benefit should therefore be carefully weighed, in consultation with the patient, when prescribing HRT to women with a risk factor for VTE. Generally recognised 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 disposition), and obesity (body mass index $> 30 \text{ kg/m}^2$). The risk of VTE also increases with age. Extensive varicose veins and superficial thrombophlebitis may have a role in VTE. The risk of VTE 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 HRT. If feasible, oestrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilisation.

Treatment should be stopped at once if there are symptoms of a thrombotic event or suspicion thereof. Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; "acute" abdomen.

Arterial Thromboembolism

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

Breast Cancer

The use of oestrogens alone as well as combined/sequential oestrogen and progestogen use for several years is associated with an increased risk of breast cancer. This emerges towards the end of the first year of treatment.

A meta-analysis from 51 epidemiological studies reported that there is a modest increased risk of having breast cancer diagnosed in women who have used HRT for more than 5 years. The findings may be due to an earlier diagnosis, the biological effects of HRT, or a combination of both. The relative risk increases with duration of treatment (by 2.3% per year of use) and may be lower or possibly neutral with oestrogen only products. This is comparable to the increased risk observed in women with every year of delay of natural menopause (2.8% per year of delay). The increased risk gradually disappears during the course of the first 5 years after cessation of HRT. Breast cancers found in women using HRT are more likely to be localised to the breast than those found in non-users (see "*WHI Study*" below). Data regarding spread outside the breast are non-conclusive. The role of progestogens in the risk of breast cancer is unclear.

HRT increases the density of mammographic images which may adversely affect the radiological detection of breast cancers in some cases. This may have implications for the sensitivity and specificity of breast cancer screening. All women should undertake yearly breast examinations and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors and prior mammogram results.

Endometrial Cancer

Prolonged exposure to unopposed oestrogens in women with intact uteri increases the risk of endometrial hyperplasia and carcinoma in postmenopausal women. Studies have suggested that the addition of a progestogen to the regimen reduces the risk of endometrial hyperplasia and/or cancer. Oestrogen or oestrogenic compounds must not be used alone as hormone replacement therapy in women who have not had a hysterectomy. Close clinical surveillance of all women taking oestrogens 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. There is no

evidence that the use of natural oestrogens results in a different endometrial risk profile than synthetic oestrogens of equivalent oestrogen dose.

Addition of a progestogen when a woman has not had a hysterectomy.

Studies of the addition of a progestogen for 10 or more days of a cycle of oestrogen administration, or daily with oestrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestogens with oestrogens compared to oestrogen-alone regimens. These include: a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g. lowering HDL, raising LDL) and impairment of glucose tolerance.

Ovarian Cancer

An increased risk of ovarian cancer in menopausal women taking oestrogen only replacement therapy was observed in a large US study enrolling over 40,000 women on HRT. These women were followed up for a mean duration of 13.4 years (range 1 month to 19.8 years). The increased risk of ovarian cancer in those taking oestrogen replacement therapy was 80%, RR 1.8 (95% CI, 1.1 - 3.0) at 10 to 19 years. This risk increased with duration of use; RR for 20 or more years of use was 3.2 (95% CI, 1.7 - 5.7). This equates to approximately 3 and 8 additional cases per 10,000 women-years at these time points; (the incidence of ovarian cancer in non-users was 4.4 per 10,000 women years). This observation was most obvious on those women on long-term oestrogen replacement therapy who had a prior history of hysterectomy (defined as simple hysterectomy or hysterectomy with unilateral oophorectomy). In this subpopulation, the RR was 2.0 (95% CI, 0.96 - 4.3) for between 10 and 19 years of use and 3.4 (95% CI, 1.6 - 7.5) for 20 years or more.

The influence of HRT on ovarian cancer is not clear. Scientific results are contradictory. The epidemiological study by Lacey et al. (as summarised above) found a slightly increased risk of ovarian cancer for women on long-term (more than 10 years) oestrogen replacement therapy while a meta-analysis of 15 studies by Coughlin et al. did not find an increased risk for women on oestrogen replacement therapy.

Liver Tumour

In rare cases benign, and in even rarer cases, malignant liver tumours leading in isolated cases led to life-threatening intra-abdominal haemorrhage have been observed after use of hormonal substances such as the one contained in CLIMARA. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnostic considerations.

Gallbladder Disease

Oestrogens are known to increase the lithogenicity of the bile. Some women are predisposed to gallbladder disease during oestrogen therapy. A two- to four-fold increase in the risk of gall bladder disease in women receiving oral oestrogens (including oral contraceptives) has been reported.

Dementia

The Women's Health Initiative Memory Study (WHIMS), a sub-study of WHI, reported an increased risk of developing probable dementia in post menopausal women 65 years of age or older during four years of treatment with oral conjugated oestrogens plus medroxyprogesterone acetate relative to placebo. 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 HRT products.

WHI Studies and Million Women Study

In a prospective randomised US clinical trial involving 8506 postmenopausal women who received oral hormone replacement therapy (HRT) using a continuous combined regimen of conjugated equine oestrogens (conjugated oestrogens) 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day and 8102 women who received placebo for an average of 5.2 years, adverse effects on the cardiovascular system and the incidence of breast cancer were observed. The Women's Health Initiative (WHI) study was designed to investigate the efficacy and safety of long-term HRT in preventing coronary heart disease (CHD) in healthy postmenopausal women with an intact uterus. A global index summarising the balance of risks and benefits included an analysis of the primary outcome of CHD and the primary adverse outcome of invasive breast cancer, and the following secondary outcomes: stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. The women enrolled in the study had a mean age at entry of 63.3 years. On average they were overweight (mean body mass index [BMI] = 28.5) and one-third were obese (BMI \geq 30), 50% were previous or current smokers, one-third had received treatment for high blood pressure and over 10% had raised cholesterol levels requiring medication.

After a mean of 5.2 years of follow-up, the study was stopped prematurely because the preset criterion for invasive breast cancer was fulfilled and the global index supported risks exceeding benefits. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02 - 1.63); breast cancer, 1.26 (1.00 - 1.59); stroke, 1.41 (1.07 - 1.85); PE, 2.13 (1.39 - 3.25); colorectal cancer, 0.63 (0.43 - 0.92); endometrial cancer, 0.83 (0.47 - 1.47); hip fracture, 0.66 (0.45 - 0.98), and death due to other causes, 0.92 (0.74 - 1.14). Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09 - 1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90 - 1.17) for total cancer and 1.15 (1.03 - 1.28) for the global index. The HR for total fractures was 0.76 (0.69 - 0.85) while total mortality was unchanged [0.98 (0.82 - 1.18)].

In this study, the absolute excess risks per 10,000 person-years attributable to oestrogen plus progestin were small, i.e. 7 more cases of CHD (37 vs 30), 8 more strokes (29 vs 21), 8 more pulmonary emboli (15 vs 7) and 8 more invasive breast cancers (38 vs 30), while the absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers (10 vs 16), 1 less endometrial cancer (5 vs 6), 5 fewer hip fractures (10 vs 15), 44 fewer total fractures (147 vs 191) and one less death (52 vs 53) than in women not using that form of HRT.

In the Million Women Study 1,084,110 women were followed up for cancer incidence and death. The average age of the women at recruitment was 55.9 years, and the average period of follow-up was 2.6 years for the analyses of cancer incidence and 4.1 years for the analyses of mortality. Overall 50% of the study population had used HRT at some point. There were 9,364 newly diagnosed cases of invasive breast cancer and 637 breast cancer deaths. Current users of HRT at recruitment were more likely to develop breast cancer and die from it than patients who had never used HRT. Patients who had used HRT previously but were no longer using it were however not at an increased risk of newly diagnosed or fatal disease. The incidence was significantly increased for current users of preparations containing oestrogen only, oestrogen/progestogen and tibolone, but the magnitude of the associated risk was greater for the combined treatment than for other types of HRT.

Relative risk of newly diagnosed invasive breast cancer in relation to recency and type of HRT used

HRT use at baseline	Cases/population	Relative risk (95% FCI)*
All never users	2894/392,757	1.00 (0.96 - 1.04)
All past users	1044/150,170	1.01 (0.95 - 1.08)
Current users of:		
Oestrogen only	991/115,383	1.30 (1.22 - 1.38)
Oestrogen – progestogen	1934/142,870 184/18,186	2.00 (1.91 - 2.09) 1.45 (1.25 - 1.67)
Tibolone	93/9548	1.44 (1.17 - 1.76)

FCI = floated CI. *Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region and deprivation index.

Results varied little between specific oestrogens and progestogens or their doses, or between continuous or sequential regimens. The relative risks were significantly increased separately for oral, transdermal and implanted oestrogen-only formulations. In terms of absolute risk, after ten years of HRT use it is estimated that there would be 5 (95% CI 3 - 7) additional cases of

breast cancer per 1000 users of oestrogen-only preparations, and 19 (95% CI 15-23) additional cases of breast cancer per 1000 users of oestrogen-progestogen combinations. The elevated risk reduces after discontinuation of HRT and is effectively lost after five years.

In the HRT subset of WHI a 26% increase in invasive breast cancer (38 vs 30 per person-years) after an average of 5.2 years of treatment was observed in women receiving the oestrogen/progestogen combination compared to women receiving placebo. The increased risk of breast cancer became apparent after four years on study medication. Women reporting prior postmenopausal hormone use had a higher relative risk for breast cancer associated with HRT than those who had never used postmenopausal hormones.

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported a two-fold increase in the risk of developing probable dementia in postmenopausal women 65 years of age or older (n = 4,532, 54% older than 70) during four years of treatment with oral conjugated oestrogens plus medroxyprogesterone acetate relative to placebo. After an average follow-up of four years the absolute risk of probable dementia was 45 per 10,000 person-years in the oestrogen plus progestogen group and 22 per 10,000 person-years in the placebo group. It is not known whether these findings apply to younger postmenopausal women.

The risks and benefits in women receiving treatment for the short-term management of menopausal symptoms of oestrogen deficiency or for the management of premature menopause were not examined in the WHI and WHIMS studies. As well, the studies did not include other formulations, dosage regimens or routes of administration of HRT; such as transdermal patches containing oestradiol. However, in the absence of comparable data, these risks should be assumed to be similar. If prescribing any form of hormone replacement therapy, the potential for increased cardiovascular, thrombotic and neoplastic adverse events must be considered.

Other Conditions

Since prolonged use of oestrogens influences the metabolism of calcium and phosphorous CLIMARA should be used with caution in women with metabolic bone disease associated with hypercalcaemia. Also, patients with pre-existing hypercalcaemia, serum calcium levels should be carefully monitored.

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.

In patients with pre-existing hypertriglyceridaemia, oestrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

A general association between HRT use and development of clinical hypertension has not been established. There have been occasional reports

of elevated blood pressure with the use of transdermal oestradiol patches in the menopause; therefore blood pressure should be monitored.

Oestrogens may be poorly metabolised in patients with impaired liver function. Caution is advised in patients with a long history of oestrogen related jaundice. If cholestatic jaundice develops in a patient receiving oestrogen, treatment should be discontinued while the cause is investigated.

Non-severe disturbances of liver function, including hyperbilirubinaemias such as Dubin-Johnson syndrome or Rotor syndrome, need close supervision and liver function should be checked periodically. In case of deterioration of markers of liver function, use of HRT should be stopped.

Although HRT may have an effect on peripheral insulin resistance and glucose tolerance, there is generally no need to alter the therapeutic regimen in diabetics using CLIMARA. However, it is recommended that diabetic patients requiring combined treatment should be kept under special surveillance.

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 whilst taking HRT.

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

Pre-existing fibroids may increase in size under the influence of oestrogens. If this is observed, CLIMARA treatment should be discontinued.

Should endometriosis be reactivated during treatment with CLIMARA, discontinuation of therapy is recommended.

Pre-Clinical Safety Data

In primary dermal irritation studies in rabbits, application of CLIMARA resulted in mild irritation related to mechanical trauma at removal. In sensitisation studies in guinea pigs, CLIMARA patches had no dermal sensitising potential.

The components of the adhesive matrix of CLIMARA (monomer and polymer) have been studied extensively and, at many times the projected human exposure, present a low risk. Additional excipients used in the adhesive matrix are either generally regarded as safe for use in food components or considered acceptable as an inactive ingredient for prescription and topical transdermal products.

The adhesive backing and release liner of CLIMARA patches were tested using biological test methods and were considered to be compatible with biological systems.

Animal toxicity studies with repeated administration, including tumourigenicity studies, did not suggest a particular risk related to use in humans. However, it should be borne in mind that sex steroids might stimulate the growth of certain hormone-dependent tissues and tumours.

In vitro and *in vivo* studies with 17 β -oestradiol gave no indications of a mutagenic potential.

Reproductive toxicity studies with oestradiol valerate did not indicate a teratogenic potential. As no non-physiological plasma concentrations of oestradiol are produced by administration of oestradiol valerate, this preparation does not present a risk to the fetus.

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction.

Use in Pregnancy

Pregnancy Category B1. Oestrogens must not be used during pregnancy (see “*Contraindications*”). If pregnancy occurs during medication with CLIMARA, treatment should be withdrawn immediately.

Use in Lactation

Oestrogens must not be used during lactation (see “*Contraindications*”). Small amounts of sex hormones may be excreted in human milk.

Use in Geriatrics

Of the total number of subjects in the conjugated equine oestrogens in combination with medroxyprogesterone acetate sub-study of the WHI study, 44% (7320) were 65 years and over, while 6.6% (1095) were 75 years and over. No significant differences were observed between subjects 65 years and over compared to younger subjects. There was a higher incidence of stroke and invasive breast cancer in women 75 years and over compared to younger subjects.

In the Women’s Health Initiative Memory Study, including 4532 women 65 years of age and older followed up for an average of four years, 71% (3762) were 65 - 74 while 18% were 75 and over. Most women (80%) had no prior HRT use. Women treated with 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Ninety percent of cases of probable dementia occurred in the 54% of women that were older than 70.

Effects on Driving or Using Machinery

CLIMARA is unlikely to produce any effect on the ability to drive or use machinery

Adverse Effects

Serious undesirable effects associated with the use of hormone replacement therapy have been referred to in the “*Contraindications*” and “*Warnings and Precautions*” sections.

Clinical Trials

In clinical trials adverse reactions were reported at the frequencies reported below:

- very common $\geq 1/10$
- common $\geq 1/100$ and $< 1/10$
- uncommon $\geq 1/1000$ and $< 1/100$

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 listed in the table below:

System Organ Class	Very Common $\geq 1/10$	Common $\geq 1/100$ and $< 1/10$	Uncommon $\geq 1/1000$ and $< 1/100$
Application site	Application site reaction, tape site reaction		
Autonomic nervous system		Increased sweating	
Body as a whole		Headache, oedema, back pain, fatigue, pain	
Cardiovascular			Tachycardia
Central and peripheral nervous system		Dizziness	Muscle cramps
Gastrointestinal system		Abdominal pain, flatulence, nausea	
Metabolic and nutritional		Alteration in body weight	
Psychiatric		Depressive moods, nervousness	
Reproductive		Breast pain, changes in uterine	Breast enlargement

		bleeding pattern (including breakthrough bleeding and spotting), endometrial hyperplasia, leucorrhoea, pelvic pain, uterine disorder, uterine spasm, vaginal disorder, vaginal moniliasis,	
Skin and appendages		Acne, pruritis, rash	

In addition to the above adverse reactions, the following adverse reactions are also known to be oestrogen related and therefore may be associated with CLIMARA therapy:

System Organ Class	Adverse Event
Central nervous system	Migraine
Gastrointestinal system	Vomiting, cholestatic jaundice, increased incidence of gallbladder disease, abdominal cramps, bloating
Cardiovascular system	Rise in blood pressure in susceptible individuals
Haematological	Thromboembolism and thrombotic disorders (see " <i>Warnings and Precautions</i> ")
Genitourinary system	Increase in size of uterine leiomyomata, alterations in the amount of cervical secretion, change in cervical erosion, reactivation of endometriosis, cystitis-like syndrome
Skin	Chloasma or melasma which may persist after the medicine is discontinued, allergic contact dermatitis, post-inflammatory pruritis, haemorrhagic eruptions, erythema nodosum, erythema multiforme, rash
Miscellaneous	Worsening of porphyria, changes in libido, premenstrual-like syndrome

Ocular	Steepening of corneal curvature, intolerance of contact lenses
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In women with hereditary angioedema, exogenous oestrogens may induce or exacerbate symptoms of angioedema (see “*Warnings and Precautions*”).

Interactions

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

Interaction with medicines

Interaction studies have not been performed with CLIMARA patches or with other oestradiol transdermal systems. As for other steroid hormones it may be anticipated that medicines which induce microsomal liver enzymes such as antiepileptics, antibiotics or products containing St. John’s Wort (*Hypericum perforatum*), could reduce the systemic bioavailability of transdermal oestradiol. However, it is probable that the systemic bioavailability of transdermally applied oestradiol is less affected by such an interaction than that of orally applied oestrogens. The requirement for oral antidiabetics or insulin can change.

Interaction with alcohol

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

Interaction with laboratory tests

The use of sex steroids may influence the results of certain laboratory tests, including biochemical parameters of 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.

Overdosage

Oestrogen overdosage is unlikely with this type of application.

Symptoms

Overdosage may cause nausea and vomiting and withdrawal bleeding may occur in some women. There is no specific antidote. Signs of overdosage may be one or more of the following: breast discomfort, breakthrough bleeding, fluid retention and bloating (see “*Dosage and Administration*”). Toxicity is unlikely following acute single exposure; ingestion may cause nausea and vomiting.

Treatment

Treatment should be symptomatic and the patch(es) should be removed

Pharmaceutical Precautions

Shelf life: 3 years

Special precautions for storage: Store below 30 °C. Do not store unpouched. Apply immediately upon removal from the protective pouch.

Medicine Classification

Prescription Medicine

Package Quantities

Packs containing 4 patches individually wrapped in a protective pouch. The pouch contains desiccant.

Further Information

Description: A protective pouch containing a CLIMARA 50 patch with a surface area of 12.5 cm² or a CLIMARA 100 patch with a surface area of 25 cm². The patches comprise two layers. From the visible surface to the surface attached to the skin these are: a translucent polyethylene film; a medicine reservoir of oestradiol in an acrylate adhesive matrix; a protective liner of release-coated polyester film which is attached to the adhesive surface and must be removed prior to use. The protective pouch contains a desiccant.

List of excipients

Ethyl oleate, isopropyl myristate, glycerol monolaurate, acrylate copolymer

Incompatibilities

No known incompatibility

Instructions for use/handling

Store all medicines properly and keep them out of reach of children.

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Date of Preparation

31 May 2008