IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1410/015/003
Case No: 2029216

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Bayer Limited

The Atrium, **Blackthorn Road**, **Dublin 18**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Climara 25 micrograms/24 hours Transdermal Patch

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **15/04/2008**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Climara 25 micrograms/24 hours Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 6.5cm^2 patch contains 1.97 mg estradiol (formed from 2.04 mg estradiol hemihydrate), releasing a nominal 25 micrograms of estradiol per 24 hours.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

Oval transdermal patch with a translucent homogenous matrix on a transparent carrier film.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women more than 1 year postmenopause.

The experience treating women older than 65 years is limited.

See also section 4.4.

4.2 Posology and method of administration

• Posology
Climara is an oestrogen-only patch applied to the skin once weekly.
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used. Treatment to control menopausal symptoms should be initiated with the lowest Climara patch dose. If considered necessary, a higher dosed patch should be used. In women with an intact uterus, a progestogen should be added to Climara for at least 12 – 14 days each month. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

For continuous use: The patches should be applied once weekly on a continuous basis, each used patch being removed after 7 days and a fresh patch applied to a different site.

For cyclical use: The patches may also be prescribed on a cyclical basis. Where this is the preferred option, the patches should be applied weekly for 3 consecutive weeks followed by a 7-day interval, without a patch being applied, before the next course.

• How to start Climara

Women who do not take oestrogens or women who change from a continuous combined HRT product may start treatment at any time.

Patients changing from a continuous sequential HRT regimen, should begin the day following completion of the prior regimen.

Patients changing from a cyclic HRT regimen should begin the day after the treatment-free period.

• Missed or lost patch
In the event that a patch falls off before 7 days are up, it may be reapplied. If necessary, a new patch should be applied for the remainder of the 7-day dosing interval.

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

After several days without replacement of a new patch there is an increased likelihood of breakthrough bleeding and spotting.

• Mode of application
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 or buttocks. 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.

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.

Children
Not recommended for children

4.3 Contraindications

- Known, past or suspected breast cancer
- Known or suspected oestrogen dependent malignant tumours e.g. endometrial cancer
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Porphyria
- Known hypersensitivity to estradiol or to any of the excipients

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Medical examination/follow-up

• Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see ‘Breast cancer’ below).

Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which require supervision

If any of the following conditions are present, have occurred previously and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Climara 25, in particular:
-Leiomyoma (uterine fibroids) or endometriosis
-A history of, or risk factors for, thromboembolic disorders (see below)
-Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
-Hypertension
-Liver disorders (e.g. liver adenoma)
-Diabetes mellitus with or without vascular involvement
-Cholelithiasis
-Migraine or (severe) headache
-Systemic lupus erythematosus
-A history of endometrial hyperplasia (see below)
-Epilepsy
-Asthma
-Otosclerosis
-Hereditary angioedema

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

-Jaundice or deterioration in liver function
-Significant increase in blood pressure
-New onset of migraine-type headache
-Pregnancy

Endometrial hyperplasia

- The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.
- Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.
- Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

Breast cancer

- A randomised placebo-controlled trial, the Women's Health Initiative study (WHI) and epidemiological studies, including the Million Women Study (MWS) have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years (see Section 4.8). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

- In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration.

- In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.
- HRT, especially oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

- HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users, it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.
- Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

- There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS, i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke

- One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 women per 1000 women aged 60-69 years. It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer

Long-term (at least 5-10 years) use of oestrogen only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than oestrogen-only products.

Other conditions

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Climara 25 is increased.
- Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex- hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).
- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger postmenopausal women or other HRT products.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbitol, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St. John's wort (Hypericum perforatum) may induce the metabolism of oestrogens.

At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens might be less affected than oral hormones by enzyme inducers.
Clinically, an increased metabolism of oestrogens may lead to decreased effect and changes in the uterine bleeding profile.

4.6 Pregnancy and lactation

• Pregnancy

Climara is not indicated during pregnancy. If pregnancy occurs during medication with Climara treatment should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

• Lactation

Climara is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Climara has no influence on the ability to drive and use machines.

4.8 Undesirable effects

During the first few months of treatment, breakthrough bleeding, spotting and breast tenderness or enlargement can occur. These are usually temporary and normally disappear after continued treatment. The table below lists adverse drug reactions recorded in clinical studies as well as adverse drug reactions reported post-marketing. Adverse drug reactions were recorded in 3 phase III clinical studies (n = 219 women) and considered at least possibly related to treatment with 25 µg/day estradiol following transdermal application.

Organ system	Adverse drug reactions reported in clinical trials		Adverse drug reactions reported post marketing
	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1000, < 1/100)	
BODY AS A WHOLE	Laboratory test abnormal.	Pain in back or extremity, asthenia[1].	
CARDIOVASCULAR SYSTEM		Migraine[1], hypertension[1], tachycardia[1]	
DIGESTIVE		Nausea, diarrhoea, flatulence[1], abnormal liver function test[1].	
IMMUNE SYSTEM DISORDERS			Exacerbation of hereditary angioedema
METABOLIC AND NUTRITIONAL	Localized or generalised oedema.	Weight gain.	
MUSCULOSKELETAL SYSTEM		Arthralgia[1],	Muscle cramps
NERVOUS SYSTEM	Headache.	Hot flushes, dizziness[1].	Paraesthesia, Insomnia, Night sweats
SKIN and APPENDAGES	Application site reaction, skin disorder, breast pain	Rash skin disorder, alopecia[1], dry skin[1], skin discoloration[1], erythema nodosum[1], benign breast neoplasm[1]	
SPECIAL SENSES		Taste disturbance[1],	
UROGENITAL	Leucorrhoea, urinary disorder, vaginal bleeding.	cervical smear changes, candidiasis, dyspareunia[1], uterine disorder[1], vaginal dryness[1].	

[1] have been reported in single cases. Given the small study population (n=219) it cannot be determined based on these results if these events are uncommon or rare.

Breast cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For *oestrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95% CI 1.21-1.49) and 1.30 (95% CI 1.211.40), respectively.

For *oestrogen plus progestogen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.
The MWS reported that, compared to never users, the use of various types of oestrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95% CI: 1.88-2.12) than use of oestrogens alone (RR = 1.30, 95% CI: 1.21-1.40) or use of tibolone (RR = 1.45, 95% CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95% CI 1.01-1.54) after 5.6 years of use of oestrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 current or recent users of HRT, the number of additional cases during the corresponding period will be
  - For users of *oestrogen-only* replacement therapy
  - between 0 and 3 (best estimate = 1.5) for 5 years' use
  - between 3 and 7 (best estimate = 5) for 10 years' use.
  - For users of *oestrogen plus progestogen* combined HRT,
  - between 5 and 7 (best estimate = 6) for 5 years' use
  - between 18 and 20 (best estimate = 19) for 10 years' use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *oestrogen-progestogen combined* HRT (CEE + MPA) per 10,000 women years. According to calculations from the trial data, it is estimated that:

- For 1000 women in the placebo group,
  - about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1000 women who used *oestrogen + progestogen combined* HRT (CEE + MPA), the number of *additional* cases would be
  - between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4).

Endometrial cancer
In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2- to 12-fold greater compared with non-users. Adding a progestogen to oestrogen-only therapy greatly reduces this increased risk.

Other adverse reactions have been reported in association with oestrogen/progestogen treatment:

-Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer.

-Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see section 4.3 Contraindications and 4.4 Special warnings and precautions for use.

-Myocardial infarction and stroke (see also section 4.4).

-Gall bladder disease.

-Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.

-Probable dementia (see section 4.4).

4.9 Overdose

Overdosage is unlikely with this type of application. Nausea, vomiting and withdrawal bleeding may occur in some women. There is no specific antidote and treatment should be symptomatic. The patch(es) should be removed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural and semisynthetic oestrogens, plain

ATC code: G03CA03

The active ingredient of Climara, synthetic 17ß-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.

Relief of menopausal symptoms was achieved during the first few weeks of treatment.

5.2 Pharmacokinetic properties

Absorption
After dermal application of Climara, estradiol is continuously released and transported across intact skin leading to sustained circulating levels of estradiol during a 7-day treatment period. The systemic availability of estradiol after transdermal administration is about 20 times higher than that after oral administration. This difference is due to the absence of first pass metabolism when estradiol is given by the transdermal route. The major pharmacokinetic parameters of estradiol are summarised in the following table:

Transdermal Delivery System	Daily Delivery Rate, mg/day	Application Site	AUC(0-Tlast) ngxh/mL / nmolxh/L	Cmax pg/mL / pmol/L	Cavg pg/mL / pmol/L	tmax h	Cmin pg/mL / pmol/L
Climara 25	0.025	Abdomen	3.57 / 13	31 / 114	21 / 77	31	17 / 63

Distribution
The distribution of exogenous oestrogens is similar to that of endogenous oestrogens. The apparent volume of distribution of estradiol after single intravenous administration is about 1 l/kg. Oestrogens circulate in the blood largely bound to serum proteins. About 61 % of estradiol is bound non-specifically to serum albumin and about 37 % specifically to sex hormone binding globulin (SHBG).

Metabolism
The biotransformation of the transdermally administered estradiol is the same as that of the endogenous hormone: Estradiol is mainly metabolised in the liver but also extrahepatically e.g. in gut, kidney, skeletal muscles and target organs. These processes involve the formation of estrone, estriol, catecholoestrogens and sulphate and glucuronide conjugates of these compounds, which are all less oestrogenic or even nonoestrogenic.

Excretion
The total serum clearance of estradiol following single intravenous administration, shows high variability in the range of 10-30 ml/min/kg. Estradiol and its metabolites are excreted in the bile and undergo a so-called enterohepatic circulation. Ultimately estradiol and its metabolites are mainly excreted as sulfates and glucuronides with the urine.

Steady-state conditions
Accumulation of estradiol and estrone was not observed following multiple 1week patch applications of higher strengths of Climara. Accordingly, steady-state serum levels of estradiol and estrone correspond to those observed after a single application.

5.3 Preclinical safety data

The toxicity profile of estradiol is well known. There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

In primary dermal irritation studies in rabbits, application of the Climara patch resulted in mild irritation related to mechanical trauma at removal. In sensitisation studies the Climara patch had no dermal sensitising potential.

Studies on the components (adhesive matrix, backing and release liner) did not indicate any risk related to the use of the Climara patch.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adhesive matrix: Isooctyl acrylate/acrylamide/vinyl acetate copolymer, ethyl oleate, isopropyl myristate, glycerol monolaurate

Adhesive backing film: polyethylene

Protective release liner (removable): polyethylene terphthalate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store below 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Each patch is sealed in a multilaminate pouch containing a desiccant. The pouch consists of polyester/aluminium/acrylonitril, methyl acrylate copolymer (BAREX210). The desiccant consists of sodium alumino silicate; pack of 4 or 12 patches (not all pack sizes may be marketed).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

After use the patch still contains substantial quantities of estradiol, which may have harmful effects if reaching the aquatic environment. Therefore, the used patch should be discarded carefully. Any used or unused patches should be folded in half, adhesive sides together, and disposed of in the solid waste disposal system. Used patches should not be flushed down the toilet nor placed in liquid waste disposal systems.

7 MARKETING AUTHORISATION HOLDER

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18

8 MARKETING AUTHORISATION NUMBER

PA 1410/15/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th May 2006

Date of last renewal: 15th April 2007

10 DATE OF REVISION OF THE TEXT

April 2008