Core Safety Profile

Active substance: Estradiol
Pharmaceutical form(s)/strength: oral and transdermal preparations
P-RMS: UK/H/PSUR/0072/001
Date of FAR: 05.12.2012
CSP

**Estradiol valerate**
oral tablets

**Estradiol hemihydrate**
Transdermal Patch
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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 or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- **Known thrombophilic disorders (eg. Protein C, Protein S, or antithrombin deficiency, see section 4.4)**
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease as long as liver functions have failed to return to normal
- Known hypersensitivity to the active substance or any of the excipients
- Porphyria

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.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favorable than in older women.

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 appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need 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, in particular:
  - leiomyoma (uterine fibroids) or endometriosis
  - 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
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 and carcinoma**

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

- The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non hysterectomised women prevent the excess risk associated with oestrogen-only HRT.

- For oral doses of estradiol >2mg, conjugated equine oestrogens >0.625 mg and patches >50 ug/day the endometrial safety of added progestagens has not been demonstrated.

- 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**

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.

**Combined oestrogen-progestagen therapy**

- The randomised placebo-controlled trial the (Women’s Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years (see Section 4.8).

**Oestrogen-only therapy**

- The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment

HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.
Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller, risk (see Section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE and HRT may add to this risk.
- Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.
- As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is ‘severe’ (e.g., antithrombin, protein S, or protein C deficiencies or a combination of defects) Climara should only be used after careful risk/benefit evaluation.
- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- 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 protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT.

Combined oestrogen-progestagen therapy:
The relative risk of CAD during use of combined oestrogen-progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen-progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Oestrogen-only:
Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.
Ischaemic Stroke

- Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Other conditions

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

- 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-1-antitrypsin, ceruloplasmin).

- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

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. phenobarbital, phenytoin, carbamezapin) 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 and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

4.6 Pregnancy and lactation

- Pregnancy

Tradename is not indicated during pregnancy. If pregnancy occurs during medication with Tradename 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
Tradename is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

**Explanatory note:**

The below information should only be included in the SmPC of relevant products to allow deviations when implementing the CSP for different products.

More than X patients have been treated with Tradename in clinical trials.

Serious undesirable effects associated with the use of hormone replacement therapy are also mentioned in section 4.4 Special warnings and precautions for use.

The table below reports undesirable effects, that have been reported in users of hormone replacement therapy (HRT) by MedDRA system organ classes (MedDRA SOCs).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common (≥1/100, &lt;1/10)</th>
<th>Uncommon (≥1/1,000, &lt;1/100)</th>
<th>Rare &lt;1/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity reaction</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight increase or Weight decrease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depressed mood</td>
<td>Anxiety, Libido decreased or Libido increased</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
<td>Migraine</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disturbances</td>
<td>Contact lens intolerance</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, Nausea</td>
<td>Dyspepsia</td>
<td>Bloating, Vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash, Pruritus</td>
<td>Erythema nodosum, Urticaria</td>
<td>Hirsutism, Acne</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td>Muscle cramps</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uterine/Vaginal bleeding including Spotting</td>
<td>Breast pain, Breast tenderness</td>
<td>Dysmenorrhea, Vaginal discharge, Premenstrual-like syndrome, Breast enlargement</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>Edema</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>
The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

<p>| Million Women study – Estimated additional risk of breast cancer after 5 years’ use |
|---------------------------------|---------------------------------|-----------------|</p>
<table>
<thead>
<tr>
<th><strong>Age range (years)</strong></th>
<th><strong>Additional cases per 1000 never-users of HRT over a 5 year period</strong></th>
<th><strong>Risk ratio #</strong></th>
<th><strong>Additional cases per 1000 HRT users over 5 years (95% CI)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oestrogen only HRT</strong></td>
<td>9-12</td>
<td>1.2</td>
<td>1-2 (0 - 3)</td>
</tr>
<tr>
<td><strong>Combined oestrogen-progestagen</strong></td>
<td>9-12</td>
<td>1.7</td>
<td>6 (5 - 7)</td>
</tr>
</tbody>
</table>

*2 Taken from baseline incidence rates in developed countries.
# Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.
Note: since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer differs by EU country; the number of additional cases of breast cancer will also change proportionately.

<p>| US WHI studies - additional risk of breast cancer after 5 year’s use |
|-------------------------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th><strong>Age range (years)</strong></th>
<th><strong>Incidence per 1000 women in placebo arm over 5 years</strong></th>
<th><strong>Risk ratio &amp; 95%CI</strong></th>
<th><strong>Additional cases per 1000 HRT users over 5 years (95% CI)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CEE oestrogen only</strong></td>
<td>21</td>
<td>0.8 (0.7-1.0)</td>
<td>-4 (-6 - 0)*3</td>
</tr>
<tr>
<td><strong>CEE + MPA oestrogen &amp; progestagens</strong></td>
<td>17</td>
<td>1.2 (1.0-1.5)</td>
<td>+4 (0 - 9)</td>
</tr>
</tbody>
</table>

*3 WHI study in women with no uterus, which did not show an increase of breast cancer.
§ When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Endometrial cancer risk

Postmenopausal women with an uterus

The endometrial cancer risk is about 5 in every 1000 women with an uterus not using HRT. In women with an uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4). Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.
Adding a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

**Ovarian cancer risk:**

Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

**Risk of venous thromboembolism:**

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

### WHI Studies - Additional risk of VTE over 5 years’ use

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Incidence per 1000 women in placebo arm over 5 years</th>
<th>Risk ratio &amp; 95%CI</th>
<th>Additional cases per 1000 HRT users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral, oestrogen-only*4</td>
<td>7</td>
<td>1.2 (0.6 - 2.4)</td>
<td>1 (-3 - 10)</td>
</tr>
<tr>
<td>Oral combined, oestrogen-progestagen</td>
<td>4</td>
<td>2.3 (1.2 - 4.3)</td>
<td>5 (1 - 13)</td>
</tr>
</tbody>
</table>

*4 Study in women with no uterus.

**Risk of coronary artery disease:**

- The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4).

**Risk of ischaemic stroke:**

- The use of oestrogen-only and oestrogen + progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.
- This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

### WHI studies combined - Additional risk of ischaemic stroke*5 over 5 years’ use.

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Incidence per 1000 women in placebo arm over 5 years</th>
<th>Risk ratio &amp; 95%CI</th>
<th>Additional cases per 1000 HRT users</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>8</td>
<td>1.3 (1.1 – 1.6)</td>
<td>3 (1 – 5)</td>
</tr>
</tbody>
</table>

*5 No differentiation was made between ischaemic and haemorrhagic stroke.

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

- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).

### 4.9 Overdose

Acute toxicity studies did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose.
Overdosage is unlikely with transdermal 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.