Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Estradiol TTS Transdermal Patch.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One transdermal patch contains 1.5 mg estradiol hemihydrate delivering 50 micrograms of estradiol in 24 hours. Patch size 15cm^2 active surface area.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Transdermal patch.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Hormone replacement therapy for oestrogen deficiency symptoms in post-menopausal women.
- Prevention of osteoporosis in post-menopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

(See also section 4.4)
The experience of treating women older than 65 years is limited.

4.2 Posology and method of adminstration

Estradiol TTS is an oestrogen-only patch that should be applied to the skin once weekly on a continuous basis, i.e. each patch is replaced with a new one after 7 days.

In women with an intact uterus the addition of a progestogen for at least 12 to 14 days per cycle is essential to help prevent any endometrial hyperplasia induced by the oestrogen. For more detailed information, please refer to section 4.4 (Special warnings and precautions for use – “Endometrial hyperplasia”).

Unless there is a previous diagnosis of endometriosis, the addition of a progestogen in hysterectomised women is not recommended.

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. Therefore, therapy should normally be started with one Estradiol TTS patch (delivering 50 micrograms of estradiol in 24 hours). If the prescribed dose does not eliminate the menopausal symptoms the dose should be adjusted stepwise after the first few months by using a transdermal patch delivering 75 or 100 micrograms estradiol per day. A maximum of 100 micrograms estradiol per day should not be exceeded. If there are persistent signs of overdose, such as breast tenderness, the dose should be reduced accordingly.

Hysterectomised women not taking HRT or transferring from another HRT product may start treatment with Estradiol TTS on any convenient day. The same holds true for non-hysterectomised women not taking HRT or transferring from a continuous combined HRT product. In non-hysterectomised women switching from sequential HRT regimens, treatment with Estradiol TTS should start after the previous treatment regimen has ended.

Consecutive new patches should be applied to different sites. It is recommended that sites are chosen below the waist

where little wrinkling of the skin occurs e.g., buttocks, hip or abdomen. Estradiol TTS must not be applied on or near the breasts. The patch should be applied to clean, dry, healthy and intact skin. The patch should be applied to the skin as soon as it is removed from its wrapping. The patch is applied by removing both parts of the protective liner and then holding it in contact with the skin for at least 30 seconds (warmth is essential to ensure maximal adhesive strength).

Should part or all of a patch detach prematurely (before 7 days) it should be removed and a new patch applied. To aid compliance it is recommended the patient then continues to change the patch on the usual day. This advice also applies if a patient forgets to change the patch on schedule. Forgetting a patch may increase the likelihood of break-through bleeding or spotting.

4.3 Contraindications

Estradiol TTS is contraindicated in:

- 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;
- Known hypersensitivity to the active substances or to any of the excipients;
- Porphyria.

4.4 Special warnings and special 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 need supervision
If any of the following conditions are present, have occurred previously and/or have been aggravated during pregnancy or pervious 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 Estradiol TTS:

- 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

Reasons for immediate withdrawal of therapy
Therapy should be discontinued if 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.
- For transdermal oestrogen patches > 50µg/day, the endometrial safety of added progestogens has not been studied.

Breast cancer
A randomized 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 randomized controlled trial and epidemiological studies found a two to three fold 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 recognized risk factors for VTE include a personal history or family history, severe obesity (Body Mass Index >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 abortions 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 post-operative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilization is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT up to six 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 randomized controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two 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 randomized 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 randomized 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 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 Estradiol TTS 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-l 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 post-menopausal 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. phenobarbital, 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.

With 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:

Estradiol TTS is not indicated during pregnancy. If pregnancy occurs during medication with Estradiol TTS, 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:

Estradiol TTS is not indicated during lactation.

4.7 Effects on ability to drive and use machines

There is no evidence from the clinical data available on oestrogen therapy to suggest that Estradiol TTS should have any effect on patient's ability to drive or operate machinery.

4.8 Undesirable effects

The most frequently reported undesirable effects (>10%) in clinical trials during treatment with Estradiol TTS were application site reactions, e.g. pruritus, erythema, eczema, urticaria, oedema and changes in skin pigmentation. They were mostly mild skin reactions and usually disappeared 2-3 days after patch removal. These effects are usually observed with transdermal oestrogen replacement therapy.

All adverse events considered to be drug-related, which were observed during the phase III (>500 patients) and Phase IV (>10,000 patients) clinical trials or from the spontaneous reporting system and literature, are summarised in the following table

Organ system class	**Common ADRs >1/100; <1/10**	**Uncommon ADRs >1/1000; <1/100**	**Rare ADRs >1/10000; <1/1000**
Skin and subcutaneous tissue		Hair changes, sweating increased	
Muscular and skeletal		Arthralgia, leg cramps	
Central & peri. nervous system	Headache	Dizziness, paresthesia, migraine	
Psychiatric disorders		Anxiety, appetite increase, depression, insomnia, nervousness	
Gastrointestinal system dis.		Nausea, dyspepsia, abdominal pain, vomiting	
Cardiovasc.		Blood pressure changes	
Myo-, endo-, pericards		Chest pain	
Vascular (extracardial)		Vein disorders	
Reproductive disease female	Breast discomfort (e.g. Mastalgia/ mastopathies, breast tenderness, breast enlargement)	Vaginal discharge, breakthrough bleeding	Worsening of uterine fibroids
Body as a whole/general dis.		Edema, fatigue, weight changes	

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: 1.21 – 1.40), 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 form the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence for 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 form the trial data, it is estimated that:

- For 1000 women n 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 use of 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 (class-effect):

- 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
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Deterioration of liver function
- Probable dementia (see section 4.4).

4.9 Overdose

The mode of administration makes significant overdose unlikely; removal of the patches is all that is required should it occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: GO3 AO3

Oestrogens
The active ingredient, synthetic 17β-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. Oestrogens prevent bone loss following menopause or ovariectomy.

Clinical Trial Information:
- Relief of menopausal symptoms was achieved during the first few weeks of the treatment. In non-hysterectomised women the bleeding profile depends on the type and dose for the progestogen and duration used in combination with Estradiol TTS.

Prevention of osteoporosis
- Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

- Evidence of the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestogen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

5.2 Pharmacokinetic properties

After application of the transdermal system containing estradiol, therapeutic concentrations of estradiol are achieved within 3 hours and maintained throughout the entire application period of the transdermal patch (7 days). Estradiol peak plasma concentrations (C_{max}) range from 59 to 155 pg/ml (baseline corrected geometric mean 92 pg/ml) and $AUC_{0\text{-}168h}$ values were between 2478 and 10694 h*pg/ml (baseline corrected geometric mean 5188 h*pg/ml). The mean average plasma concentration (C_{av}) is 42 pg/ml (range: 20 to 145 pg/ml) and mean C_{pre} (trough concentration before next patch application) is 29 pg/ml. After removal of the transdermal patch, estradiol concentrations return to pre-treatment values (below 10 pg/ml) within 12 hours.

By transdermal administration of Estradiol TTS, there is no hepatic first-pass effect and the estradiol reaches the bloodstream directly in unchanged form and in physiological amounts. With the use of Estradiol TTS the estradiol concentrations are raised to values similar to those of the early to middle follicular phase.

The liver is the major site for estradiol metabolism. The primary metabolites are estrone and estriol and their conjugates (glucuronide and sulfate). Estradiol is excreted into the urine mostly as glucuronide and sulfate. The urinary excretion approaches pretreatment levels within 24 hours after patch removal.

5.3 Preclinical safety data

No adverse effects can be predicted from animal toxicology studies other than those documented from human use of estradiol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer: Transparent polyethylene terephthalate (PET) foil.
Adhesive matrix: Styrene-isoprene-styrene block copolymer, glycerine esters of completely hydrogenated resins.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

The container (primary packaging) consists of a sealed laminated sachet. This comprises layers of food grade paper/polyethylene/aluminium/ ethylene copolymer.

Package sizes: Cartons of 1, 4, 8, 9 and 12 patches.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

After removal from the laminated sachet, peel off the two part protective liner. Try to avoid touching the adhesive. Stick the adhesive side down to the upper left or right buttock on a clean and dry area of skin. Hold the applied patch to the skin with the palm of the hand for at least 30 seconds, in order to ensure optimal adhesion to the skin.

Recommended application sites are clean, dry and intact areas of skin on the trunk below the waistline. Estradiol TTS Patch should not be applied on or near the breasts. After removal the used patch should be folded and disposed of with the normal household solid waste.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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