**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

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

**(S.I. No.540 of 2007)**

**PA0013/070/002**
Case No: 2049910

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

**Novartis Pharmaceuticals UK Ltd**

**Frimley Business Park**, **Frimley**, **Camberley**, **Surrey, GU16 7SR**, **United Kingdom**

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

**Estraderm TTS 50mcg/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 **31/05/2008**.

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

Estraderm TTS 50mcg/24 hours Transdermal Patch

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One Estraderm TTS 50 transdermal patch contains 4 mg estradiol (as hemihydrate). The patch has an absorption rate of estrodiol of approximately 50 micrograms per day from an active surface area of 10 $cm^2$.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Transdermal Patch.
A thin, round, flat transparent patch with protective release liner. The backing film is printed with the code 'CG EFE'. The outside diameter is 48 mm and the active surface area is 10 $cm^2$.

## 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.
The experience treating women older than 65 years is limited.

### 4.2 Posology and method of administration

**Adults and elderly:**

**Dosage**

For initiation and continuation of treatment in post-menopausal symptoms the lowest effective dose for the shortest duration (see also section 4.4) should be used.

In women with an intact uterus, oestrogens should always be supplemented by administration of a progestogen. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

If Estraderm TTS is used in combination with a progestogen, the interruption of treatment may increase the likelihood of recurrence of symptoms including breakthrough bleeding and spotting.

Estraderm TTS should be applied twice weekly, e.g. the system should be changed once every 3 to 4 days. Treatment is normally initiated with Estraderm TTS 50. In the further course of treatment the dosage should be individually adapted; breast discomfort, breakthrough bleeding, fluid retention (if persisting for more than six weeks) are generally signs that the dose is too high and needs to be lowered.

If, however, the dose selected fails to eliminate the signs and symptoms of oestrogen deficiency the higher dose should be given. For treatment of menopausal symptoms, the lowest effective dose should always be used. A maximum dose of 100 micrograms per day should not be exceeded.

For prevention of bone loss, Estraderm TTS 50 or Estraderm TTS 100 is recommended. Estraderm TTS 25 is not recommended for prevention of bone loss.

**Therapeutic regimen**

Estraderm TTS is administered as continuous treatment (uninterrupted application twice weekly), in women with an intact uterus, oestrogen therapy should be supplemented by sequential administration of a progestogen (e.g. medroxyprogesterone acetate 10 mg, norethisterone 5 mg, norethisterone acetate 1-5 mg, or dydrogesterone 20 mg per day) to be taken on the last 12 days of each 4 week treatment cycle. Withdrawal bleeding usually occurs following the 12 days or more of progestogen administration.

**Administration**

Immediately after removal of the protective liner, the patch should be applied to an area of clean, dry and intact skin.

The site selected should be one at which little wrinkling of the skin occurs during movement of the body, e.g. buttock, hip or, abdomen and which is not exposed to sunlight, e.g. those areas normally covered by clothing.

Experience to date has shown that less irritation of the skin occurs on the buttock than at other sites of application. It is therefore recommended to apply the patch to the buttock. The area of skin should be non-greasy and free of irritation. Estraderm TTS must NOT be applied to the breasts. The patch should not be affixed twice in succession to the same skin site.

If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The subsequent patch should be applied according to the original treatment schedule. The interruption of treatment might increase the likelihood of recurrence of symptoms.

For patches with dose of estradiol above 50 micrograms/day the endometrial safety of added progestogens have not been studied.

**Children:**

Estraderm TTS should not be used in children.

## 4.3 Contraindications

Estraderm TTS should not be used by women with any of the following conditions:

- Known, past or suspected breast cancer,
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer),
- Undiagnosed vaginal bleeding,
- Untreated endometrial hyperplasia,
- Previous idiopathic or current venous thromboembolism (VTE) (deep venous thrombosis, pulmonary embolism),
- Active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction)
- Known hypersensitivity to the active substance, or any of the excipients,
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal,
- 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 taken 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 breast 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 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 Estraderm TTS, 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. 1$^{st}$ 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**

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 progestagen 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 breakthrough 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 progestagens 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 or oestrogen-progestagen 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-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

**Venous thromboembolism (VTE)**

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/m2) 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, dyspnea).

**Coronary artery disease (CAD)**

**HRT should not be used to prevent cardiovascular disease.**

There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and 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 transdermal oestrogen-only and oestrogen-progestogen combined HRT products, there are only limited data from randomised controlled trials to date assessing the HRT-associated risk of cardiovascular morbidity or mortality.

Therefore, it is uncertain whether these findings also extend to Estraderm TTS.

**Stroke**

One large randomised clinical (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 estrogens 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.

For transdermal oestrogen-only and oestrogen-progestogen combined HRT products, there are no randomised controlled trials to date assessing the HRT-associated risk of stroke morbidity or mortality. Therefore, there are no data to support the conclusion that the frequency of stroke is different with Estraderm TTS.

**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.

**Contact sensitisation**

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

**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 Estraderm 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 oral oestrogen therapy in this condition.

Estrogens 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/rennin substrate, alpha-I antitrypsin, ceruloplasmin).

With transdermal administration, stimulation of the liver by the first-pass effect is avoided and, thus, transdermal oestrogens might affect hormone binding proteins and other serum proteins produced by the liver less than oral hormones.

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 and progestogens 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), meprobamate, phenylbutazone, and anti-infectives (eg rifampicin, rifabutin nevirapine, efavirenz).

Caution should be used if the patient is receiving protease inhibitors (e.g. ritonavir and nelfinavir), which are known as strong inhibitors of cytochrome P450 enzymes, and 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 and progestogens.

Clinically, increased metabolism of oestrogens and progestogens may lead to decreased effects and changes in the uterine bleeding profile.

With transdermal HRT administration, the first-pass effect in the liver is avoided and thus transdermally applied oestrogens and progestogens may be less affected by enzyme inducers than oral hormones.

## 4.6 Pregnancy and lactation

Estraderm TTS is not indicated during pregnancy. If pregnancy occurs during medication with Estraderm 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.

## 4.7 Effects on ability to drive and use machines

None known.

## 4.8 Undesirable effects

Transient erythema and irritation at the site of application, with or without pruritus. This usually disappears 3-4 days after patch removal and is similar to the effect observed after occlusion of the skin with household medical adhesive plasters. Additionally, breast discomfort (sign of oestrogen effect, sign of overdose) and break through bleeding were the most frequently reported undesirable effects (the latter is usually a sign of estrogen overdose); if the oestrogen is adequately combined with a progestogen, regular withdrawal bleeding occurs, as observed in the normal menstrual cycle. Like any oestrogen therapy, transdermal oestrogen treatment can induce endometrial hyperplasia unless oestrogen intake is supplemented by adequate doses of a progestogen.

Frequency estimate: Very common ≥10%; common ≥1% to 10%; uncommon ≥0.1% to < 1%; rare ≥0.01% to < 0.1%.

**Skin disorders:**
Uncommon: Local swelling, papules/vesicles and scaling have been reported, which also resolved spontaneously and did not result in permanent skin damage.

**Nervous system disorders:**
Common: headache, migraine.
Rare: dizziness.

**Gastrointestinal disorders:**
Common: nausea, abdominal cramps, bloating.

**Reproductive system and breast disorders:**
Uncommon: breast cancer (see section 4.4).

**General disorders:**
Uncommon: leg cramps (not related to thromboembolic disease and usually transient lasting 3-6 weeks, if symptoms persist, the oestrogen dose should be reduced).

Rare: Oedema, weight increase or decrease, leg pain (not related to thromboembolic disease and usually transient, lasting 3-6 weeks. If symptoms persist, the oestrogen dose should be reduced).

**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 progestagen* 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-progestagen 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-progestagen combined HRT (CEE + MPA) in all users compared to 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 progestagen* 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-progestagen 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+progestagen 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 is irrespective of age at start of HRT use (between the ages of 45 and 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 among unopposed oestrogen users varies from 2- to 12- fold greater compared with non-users. Adding a progestagen to oestrogen-only therapy greatly reduces this increased risk.

Other adverse reactions have been reported in association with oestrogen alone and oestrogen-progestogen treatments.

- Oestrogen-dependent neoplasma, benign and malignant, e.g. endometrial cancer,
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, thrombophlebitis, exacerbation of varicose veins, hypertension,
- Stroke,
- Myocardial infarction,
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura, allergic contact dermatitis, reversible post-inflammatory pigmentation; generalised pruritus and exanthema,
- Gall bladder disease,
- Cholestatic jaundice,
- Asymptomatic impaired liver function,
- Anaphylactoid reactions (history of previous allergy or allergic disorders in some cases).
- Probable dementia (see section 4.4)

## 4.9 Overdose

This is not likely due to the mode of administration.

Signs and symptoms: Signs of acute oestrogen overdosage may be either one of, or a combination of breast discomfort, fluid retention and bloating, or nausea.

Treatment: Overdosage can if necessary be reversed by removal of the patch.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormone Replacement Therapy (ATC Code G03FA01).

Estradiol: 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.

The patch formulation (transdermal therapeutic system, TTS) delivers hormone into the bloodstream via intact skin. Estraderm TTS is designed to deliver 17β-estradiol at a low rate over several days.

## 5.2 Pharmacokinetic properties

Within four hours after application of the first system, plasma estradiol levels reach the therapeutic range and these are maintained throughout the dose interval (for up to four days).

After removal of the last system plasma oestrogen levels return to baseline values in less than 24 hours and urinary oestrogen conjugates within 2-3 days.
Absorption rate may vary between individual patients. However, the plasma estradiol levels achieved with different sized systems have been shown to be proportional to the drug-releasing area of the dosage form.

## 5.3 Preclinical safety data

Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Ethanol
Hydroxypropylcellulose
Polyethylene terephthalate
Ethylene vinylacetate copolymer
Paraffin liquid, light
Polyisobutylene
Light petroleum
Silicone
Printing ink: CFA 4215 Weiss

## 6.2 Incompatibilities

**Ultra violet light (i.e. sunlight)**
Exposure of Estraderm TTS 50 Transdermal Patches to ultraviolet light results in degradation of estradiol. Patches should not be exposed to sunlight. They should be applied immediately after removal from the sachet to skin sites covered by clothes.

## 6.3 Shelf Life

2 years.

## 6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light.

## 6.5 Nature and contents of container

Cartons contain 8 Estraderm TTS 50 transdermal patches, each individually sealed in a protective pouch (i.e. Surlyn coated aluminium foil liner).

## 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

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Ltd
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## 8 MARKETING AUTHORISATION NUMBER

PA 13/70/2

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of fist authorisation: 31st May 1988
Date of last renewal: 31st May 2008

## 10 DATE OF REVISION OF THE TEXT

March 2010