

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Estracombi TTS Transdermal Patches.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Estracombi TTS is comprised of an Estraderm TTS 50 patch and an Estragest TTS patch.

- i. Estraderm TTS system contains 4 mg estradiol (as hemihydrate) with an absorption rate of approximately 50 micrograms of estradiol per day from a drug releasing area of 10cm².
- ii. Estragest TTS system contains 10 mg estradiol (as hemihydrate) and 30 mg norethisterone acetate. The absorption rates from the system are approximately 50 micrograms of estradiol per day and 250 micrograms of norethisterone acetate per day from a drug releasing area of 20cm².

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal Patch.

Estraderm TTS 50: a self-adhesive, circular, transparent, transdermal therapeutic system (patch) marked 'CG DWD'.

Estragest TTS: a self-adhesive, goggle-shaped, transparent, transdermal therapeutic system (patch) marked 'CG FNF'.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As hormone replacement therapy in patients with an intact uterus and with disorders due to natural or surgically induced menopause.

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.

4.2 Posology and method of administration

Dosage

Adults and elderly: For initiation and continuation of treatment of post-menopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4, Special warnings and precautions for use) should be used.

Estracombi TTS provides continuous oestrogen and sequential progestogen therapy to women with an intact uterus.

One treatment cycle of Estracombi TTS consists of 4 patches of transdermal estradiol (Estraderm TTS 50) followed by 4 patches of transdermal estradiol and norethisterone acetate (Estragest 250/50). Therapy is started with transdermal estradiol (Estraderm TTS 50) which should be applied twice weekly for 2 weeks, i.e. the patch should be changed once every 3 to 4 days.

For the following 2 weeks, one transdermal estradiol plus norethisterone acetate patch (Estragest TTS) should be applied twice weekly. The next treatment cycle should be started with Estraderm TTS 50 immediately after renewal of the last Estragest TTS (50/250) patch.

Each fresh patch should be applied to a slightly different site. Recommended application sites are clean, dry and intact areas of skin on the trunk below the waistline. The site selected should be one at which little wrinkling of the skin occurs during movement of the body, e.g. buttock, hip, abdomen.

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 and breakthrough bleeding and spotting.

Experience to date has shown that less irritation of the skin occurs on the buttocks than at other sites of application and this site is preferred by patients. It is therefore recommended to apply Estracombi TTS to the buttock. Estracombi TTS should NOT be applied on or near the breasts. The patch should not be affixed twice in succession to the same skin site.

Estracombi TTS incorporates a combined estrogen and progestogen patch to induce withdrawal bleeding, thereby minimising the risk of endometrial hyperplasia and carcinoma, which can occur with unopposed estrogen therapy. Most patients will bleed towards the end of progestogen therapy. A few patients will experience amenorrhoea. The first transdermal patch of the new cycle should be applied irrespective of the duration of bleeding. It is important that the patches be used in the correct sequence i.e. 2 weeks Estraderm TTS 50 followed by 2 weeks Estragest TTS each cycle, to ensure regular cyclic bleeding.

For most postmenopausal women Estracombi TTS therapy may be started at any convenient time. However, if the patient is still menstruating commencement within 5 days of the onset of bleeding is recommended.

Some breakthrough bleeding or spotting may be seen until therapy has become established. Some effects, usually of estrogenic origin, e.g. breast discomfort, water retention or bloating, are often observed at the start of treatment, especially in patients receiving hormone replacement therapy for the first time. However if symptoms persist for more than 6 weeks, treatment should be reconsidered.

The patch should not be exposed to sunlight.

The use of creams, oils or lotions should be avoided since these may reduce patch adhesion.

4.3 Contraindications

Estracombi 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 abnormal 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)
- 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 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 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 reinstating 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 aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised.

- 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 in case a contraindication 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

Osteoporosis

When initiating HRT for the prevention of osteoporosis, careful consideration should be given to the benefits versus the risks for the individual. Potential alternative therapies should be considered if the risks outweigh the benefits. Periodic re-evaluation for continuing treatment is recommended.

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.

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 i.e. Women's Health Initiative 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 Estracombi.

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 five 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.

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

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 use 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 mobile. 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).

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 oestrogen or oestrogen-progestogen combinations or tibolone for HRT for several years (see section 4.8, Undesirable effects).

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 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.

Endometrial Hyperplasia

The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see section 4.8, Undesirable effects). 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 continued 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 oestrogens replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

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 Estracombi is increased.

Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement therapy or hormonal 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/renin 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 (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Caution should be used if the woman 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 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 and oral hormones.

4.6 Pregnancy and lactation

Pregnancy

Estracombi TTS is not indicated during pregnancy. If pregnancy occurs during medication with Estracombi treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens and progestagens indicate no teratogenic or foetotoxic effect.

Lactation

Estracombi TTS must not be used while breast-feeding. Oestrogens or progestogens are excreted in breast milk and may reduce the production of breast milk.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Approximately one third of women treated with Estracombi can be expected to experience adverse reactions. Most of these effects are mild and transient.

The most frequently reported adverse reactions ($\geq 10\%$) are headache, application site reactions, breast pain, breast tenderness, dysmenorrhea and menstrual disorders.

Frequency estimate: common $\geq 1\%$ to $< 10\%$, uncommon $\geq 0.1\%$ to $< 1\%$, rare $\geq 0.01\%$ to $< 0.1\%$, very rare $< 0.01\%$.

| | |
|---|--|
| <p><u>Nervous system disorders</u></p> <p><i>Common</i></p> <p><i>Rare</i></p> | <p>Headache</p> <p>Dizziness</p> |
| <p><u>Cardiovascular Disorders</u></p> <p><i>Very rare</i></p> | <p>Thromboembolic disorders, exacerbation of varicose veins, increases in blood pressure.</p> |
| <p><u>Gastrointestinal Disorders</u></p> <p><i>Common</i></p> <p><i>Very rare</i></p> | <p>Nausea, abdominal cramps, bloating</p> <p>Asymptomatic impaired liver function</p> |
| <p><u>Skin and subcutaneous tissue disorders</u></p> <p><i>Very common</i></p> <p><i>Very rare</i></p> | <p>Transient erythema and irritation at the site of application with or without pruritus.</p> <p>Allergic contact dermatitis, reversible post-inflammatory pigmentation, generalised pruritus and exanthema.</p> |

| <u>Reproductive system and breast disorders</u> | |
|---|---|
| <i>Very common</i> | Breast discomfort (1), breakthrough bleeding, spotting. |
| <i>Common</i> | Change in menstrual flow, dysmenorrhoea, premenstrual like syndrome, endometrial hyperplasia (1.5%) |
| <i>Uncommon</i> | Breast cancer |
| <u>General disorders and administration site condition</u> | |
| <i>Rare</i> (2). | Oedema, weight changes, leg pain |
| <i>Very rare</i> | Anaphylactoid reactions (3). |

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 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 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, Special warnings and precautions for use).

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 progestagen to oestrogen-only therapy greatly reduces this increased risk.

Other adverse reactions have been reported in association with some oestrogen-progestogen treatments:

- Oestrogens-dependent neoplasms, benign and malignant, e.g. endometrial cancer,
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, exacerbation of varicose veins, hypertension.
- Stroke,
- Myocardial infarction,
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia (see section 4.4, Special warnings and precautions for use).

4.9 Overdose

Due to mode of administration overdosage is unlikely.

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.

Signs of progestogen overdosage may be nausea, vomiting, breast enlargement and vaginal bleeding.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and oestrogens, sequential combinations (ATC code G03FBO5).

Estradiol

The active ingredient, synthetic 17 β -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.

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

Norethisterone Acetate

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen reduces but does not eliminate the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women. With Estragest TTS progestogen is added for the last 14 days in each cycle in order to prevent endometrial hyperstimulation. A regular cyclic bleed can be expected to start on day 24-26 of treatment.

5.2 Pharmacokinetic properties

Within four hours of application of the first Estraderm TTS 50 patch, 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 patch, plasma estrogen levels return to baseline values in less than 24 hours, and urinary estrogen conjugates within 2-3 days.

Mean plasma concentrations of estradiol are similar during both phases of the treatment (i.e. transdermal estradiol alone with Estraderm TTS 50, or transdermal oestradiol plus norethisterone acetate with Estragest TTS).

Norethisterone acetate is metabolised to the active progestogen, norethisterone, which reaches plasma levels of 0.5 - 1.0 ng/ml within 2 days after Estragest TTS application. These levels are maintained throughout the dose interval and are sufficient to prevent endometrial hyperstimulation. After removal of the system, levels of norethisterone return to baseline within 2 days.

Absorption rates may vary between individual patients.

5.3 Preclinical safety data

At low physiological doses of estradiol (similar to those delivered by Estracombi TTS), the potential of neoplasia is negligible in experimental animals. Most of the documented effects of exogenously administered estradiol in animal studies have been consequences of the administration of higher doses and are consistent with an exaggerated pharmacological response (most notably the promotion of tumours in oestrogen-responsive tissues). However, long term unopposed treatment with physiological doses of estradiol may potentially lead to hyperplastic changes in oestrogen-dependent reproductive organs like the uterus.

A similar spectrum of tumour formation is known to occur in long term laboratory animal studies with NET and NETA alone or in combination with oestrogen with some species differences. However, results from clinical studies and epidemiological evidence on the carcinogenic risk to humans are addressed under Section 4.4 'Special warnings and precautions for use'.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Hyprolose
Polyethylene terephthalate
Ethylenevinylacetate copolymer
Liquid paraffin
Polyisobutylene
Silicone
Light petroleum ether

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Estraderm systems are individually packaged in a heat-sealed sachet made of aluminium/Surlyn foil. Estragest systems are individually packaged in a heat-sealed sachet made of paper/polyethylene/aluminium/Surlyn foil. One package of Estracombi TTS comprises 4 Estraderm TTS 50 patches and 4 Estragest TTS patches.

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

Ultraviolet light (i.e. sunlight)

Exposure of the estraderm TTS and Estragest TTS patches to ultraviolet light results in degradation of estradiol and norethisterone acetate. Patches should not be exposed to sunlight. They should be applied immediately after removal from the sachet to skin sites covered by clothes.

7 MARKETING AUTHORISATION HOLDER

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