SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

EVOREL GEL 500 micrograms/actuation transdermal gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains 1.0325 mg of estradiol hemihydrate, corresponding to 1.0000 mg of anhydrous estradiol. Each dose delivers 0.5 g of gel, i.e. 0.5 mg of estradiol (as 0.516 mg of estradiol hemihydrate).

Excipient with known effect:

Propylene glycol (6.0 mg).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal gel

Clear, translucent, colourless-to-slight yellowish and odourless gel

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone Replacement Therapy (HRT) for estrogen deficiency symptoms in postmenopausal women. The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Two therapeutic regimens can be used:

1. Cyclic: for 24 to 28 days, followed by a 2 to 7 days treatment free period. The progestogen should be administered at least during the last 12 days of the estradiol treatment in non-hysterectomised women. Withdrawal bleeding may occur during this period.
2. Continuous: with no treatment free period. In non-hysterectomised women the progestogen should be administered for at least 12 days per month. Withdrawal bleeding may occur when

the progestogen is withdrawn.

3. Continuous, non-cyclic, treatment may be recommended in cases where marked symptoms of estrogen deficiency recur during the treatment-free period.
4. 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 estrogen. For more detailed information, please refer to section "Special warnings and precautions for use" – Endometrial hyperplasia).

5. In hysterectomised women, unless there is a previous diagnosis of endometriosis, the addition of a progestogen is not recommended.

Menopausal and postmenopausal symptoms
Each metered dose (1 pump actuation) from the dispenser is 0.5 g of Evorel Gel. One pump (0.5 g) of Evorel Gel once daily (0.5 mg Estradiol) is the usual starting dose for 24 to 28 days. This starting dose can be adapted per the patients' individual needs. The average dose is three pumps (1.5 g) of Evorel Gel per day, which in the majority of women will provide effective relief of symptoms.
If after one month's treatment effective relief is not obtained, the dosage may be increased accordingly to a maximum of six pumps (3 g) of Evorel Gel daily (3 mg Estradiol). The lowest effective dose should be used for maintenance therapy.

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.

Use with progestogen
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 estrogen.

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

Initiation of treatment
Women who have never taken HRT and are post-menopausal or have very infrequent menstrual cycles: treatment with Evorel Gel can be started on any day.

Switching from a continuous oestrogen-progestogen combined HRT: treatment with Evorel Gel can be started on any day of the cycle.

Switching from a cyclic or continuous sequential HRT treatment: finish the therapeutic sequence before beginning treatment with Evorel Gel.

Method of Administration

It may be necessary to prime the pump when beginning a new bottle. The pump must be pressed several times until gel comes out of the pump. The first dose may not be accurate and should be discarded. The pump may need to be reprimed after first use.

The correct dose of gel should be dispensed and applied to clean, dry, intact areas of skin *e.g.* on the arms and shoulders, or inner thighs, preferably after washing in the morning or evening. The area of application should be at least 2 times the size of the hand. Evorel Gel should NOT be applied on or near the breasts or on the vulval region. A frequent change in application sites is recommended.

It is not necessary to rub Evorel Gel in, however, it should be allowed to dry for 2 minutes before covering the skin with clothing.

Women should cover the application site with clothing if another person may come into contact with the area of skin after the gel dries. The site of application should not be washed for 60 minutes.

Patients should be informed that children should not come in contact with the area of the body where Evorel was applied on (see section 4.4).

For people not being treated with Evorel Gel:

In the event of contact with an application area, which has not been washed or is not covered with clothing, wash the area of skin onto which Evorel Gel may have been transferred as soon as possible, using soap and water.

If the patient forgets to apply a dose and it is more than 12 hours until the next dose, the missed dose should be applied and normal dosing resumed the next day. If the next dose is less than 12 hours away, it is best just to wait and apply the next dose normally. Patients should be advised not to apply two doses at the same time.

Forgetting a dose may increase the likelihood of break-through bleeding and spotting.

The individual dose can be adjusted to individual needs. Individual doses may range from 0.5 g to 3 g of gel. The average dose is 1.5 g of gel per day, i.e. 3 consecutive doses.

4.3 Contraindications

- Known, past or suspected breast cancer.
- Known or suspected estrogen-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 (e.g. 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.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 favourable 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 EVOREL GEL, in particular:

- Leiomyoma (uterine fibroids) or endometriosis.
- Risk factors for thromboembolic disorders (see below).
- Risk factors for estrogen 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 estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and estrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.
- The addition of a progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined estrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with estrogen-only HRT.
- For oral doses of estradiol > 2 mg, conjugated equine estrogens > 0.625 mg and patches > 50 µg/day the endometrial safety of added progestogens 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 estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to estrogen 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 shows an increased risk of breast cancer in women taking combined estrogen-progestogen or estrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oetrogen-progestogen therapy

- The randomised placebo-controlled trial Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8).

Estrogen – only therapy

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

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

HRT, especially estrogen-progestogen 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. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies including the WHI trial suggest that the use of combined HRTs may be associated with 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).
- Generally recognised risk factors for VTE include, use of estrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), 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.
- 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).
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients.

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 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), HRT is contraindicated.

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 estrogen-progestogen or estrogen-only HRT.

Combined oetrogen-progestogen therapy

- The relative risk of CAD during use of combined estrogen+progestogen 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 estrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Estrogen–only therapy

- Randomised controlled data found no increased risk of CAD in hysterectomised women using estrogen-only therapy.

Ischaemic stroke

Combined estrogen-progestogen and estrogen-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

- Estrogens 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 estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- 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).
- 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 estrogen-only HRT after the age of 65

ALT elevation

During clinical trials with the hepatitis C virus (HCV) combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol- containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing estrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is

warranted for co-administration with the following combination drug regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. See section 4.5.

Potential estradiol transfer

If no precaution is taken, estradiol gel can be transferred to other persons by close skin-to-skin contact. The following precautions are therefore recommended:

- for the patient:
  - wash hands with soap after applying the gel,
  - cover the application area with clothing once the gel has dried,
  - shower before any situation in which this type of contact is foreseen.
- for people not being treated with EVOREL GEL:
  - in the event of contact with an application area which has not been washed or is not covered with clothing, wash the area of skin onto which estradiol may have been transferred, using soap and water.

Potential estradiol transfer to children

Estradiol gel can be accidentally transferred to children from the area of the skin where it was applied on.

Post-marketing reports of breast budding and breast masses in prepubertal females, precocious puberty, gynaecomastia and breast masses in prepubertal males following unintentional secondary exposure to estradiol gel have been reported. In most cases, the condition resolved with removal of estradiol exposure.

Patients should be instructed:

- not to allow others, especially children, to come into contact with the exposed area of the skin and to cover the application site with clothing if needed. In case of contact the child's skin should be washed with soap and water as soon as possible.
- to consult a physician in case of signs and symptoms (breast development or other sexual changes) n a child that may have been exposed accidentally to estradiol gel.

Excipients known to have a recognized action or effect

- The presence of propylene glycol, may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of estrogens 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, carbamazepin) 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 estrogens.

At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied estrogens might be less affected than oral hormones by enzyme inducers.

Clinically, an increased metabolism of estrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

Effect of HRT with estrogens on other medicinal products

Hormone contraceptives containing estrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

Pharmacodynamic interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also with glecaprevir/pibretasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.

Women using medicinal products containing estrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is warranted for co-administration with the combination drug regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Breastfeeding

EVOREL GEL 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

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

Tabulated list of adverse reactions

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

System organ class	Common (□ 1/100; < 1/10)	Uncommon (□ 1/1,000; < 1/100)	Rare (□ 1/10,000; <1/1,000)
Immune system disorders		Hypersensitivity reaction	
Metabolism and nutrition disorders	Weight increase or weight decrease		
Psychiatric disorders		Depressed mood	Anxiety, Libido decreased or Libido increased
Nervous system disorders	Headache	Dizziness	Migraine
Eye disorders		Visual disturbances	Contact lens intolerance
Cardiac disorders		Palpitations	
Gastrointestinal disorders	Abdominal pain, Nausea	Dyspepsia	Bloating, Vomiting
Skin and subcutaneous tissue disorders	Rash, Pruritus	Erythema nodosum, Urticaria	Hirsutism, Acne
Musculoskeletal and connective tissue disorders			Muscle cramps
Reproductive system and breast disorders	Uterine/Vaginal bleeding including Spotting	Breast pain, Breast tenderness	Dysmenorrhea, Vaginal discharge, Premenstrual-like syndrome, Breast enlargement
General disorders and administration site conditions		Oedema	Fatigue

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 estrogen-progestogen therapy for more than 5 years.
- The increased risk in users of estrogen-only therapy is lower than that seen in users of estrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Absolute risk estimation based on the results of the largest randomized placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented.

Largest meta-analysis of prospective epidemiological studies - Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years) *	Risk ratio	Additional cases per 1000 HRT users after 5 years
Estrogen only HRT			
50	13.3	1.2	2.7
Combined estrogen-progestogen			
50	13.3	1.6	8.0
* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)			
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years) *	Risk ratio	Additional cases per 1000 HRT users after 10 years
Estrogen only HRT			
50	26.6	1.3	7.1
Combined estrogen-progestogen			
50	26.6	1.8	20.8
* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)			
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
CEE estrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
CEE+MPA estrogen & progestogen§			

50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

* 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 a uterus

The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.

In women with a uterus, use of estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of estrogen-only use and estrogen 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 progestogen to estrogen-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

Use of estrogen-only or combined estrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

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

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)
Oral combined estrogen-progestogen			
50-59	4	2.3 (1.2-4.3)	5 (1-13)
* Study in women with no uterus.			

Risk of coronary artery disease

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

Risk of ischaemic stroke

- The use of estrogen-only and estrogen + progestogen 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* over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1-1.6)	3 (1-5)
* No differentiation was made between ischaemic and haemorrhagic stroke.			

Other adverse reactions have been reported in association with estrogen/progestogen 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).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the **Google Play** or **Apple App Store**. By reporting side effects, you can help provide more information on the safety of this medicine.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ESTROGENS (Genitourinary system and sex hormones) ATC code: G03CA03

Mechanism of action

Natural estrogen by transdermal route

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

Clinical Trial Information

Clinical efficacy, safety and acceptability

Evorel Gel was evaluated in an open, randomised phase 3 study of 277 postmenopausal women, 145 women were treated with Evorel Gel and 132 with comparator for a period of 3 months.

Rapid and dramatic decrease in daily frequency and intensity of hot flushes was reported. No statistical significant difference for efficacy between Evorel Gel and comparator were reported.

	Evorel Gel (n=145)			Comparator (n=132)		
	Before	4 weeks	3 months	Before	4 weeks	3 months
Number of hot flushes	10.5 ± 0.4	2.7 ± 0.3	1.4 ± 0.2	10.7 ± 0.5	2.4 ± 0.3	1.6 ± 0.3
Kupperman Index	22.7 ± 0.6	9.3 ± 0.6	6.3 ± 0.5	23.0 ± 0.7	9.1 ± 0.6	7.2 ± 0.6
Visual analogue scale (mm)	66.7 ± 1.9	N/A	8.3 ± 1.4	69.5 ± 1.6	N/A	11.4 ± 1.7

For Evorel Gel, skin intolerance was reported in 2.7% of participants versus 29.0% in the comparator group, no adverse events at the application site were reported in the Evorel Gel group. Evorel Gel was considered as having good acceptability by 97% of participants versus 78% of comparator.

Relief of estrogen deficiency symptoms and bleeding patterns

Evorel Gel was evaluated in an open, randomised phase 3 study of 254 postmenopausal women, 128 receiving Evorel Gel and 126 receiving comparator for a period of 6 consecutive cycles (day 1 to 24 of each month receiving treatment) in sequential combination with nomegestrol acetate (5 mg per day from day 11 to day 24).

Relief of menopausal symptoms was achieved within the study period (3 months), with a significant decrease in frequency and intensity of hot flushes. 95% of cycles were followed by a withdrawal bleed lasting on average 5 days, breakthrough bleeding was reported in 31% of participants. Clinical tolerance of Evorel Gel was considered good.

5.2 Pharmacokinetic properties

Absorption

In a pharmacokinetic study, application a single dose of 1.5 g of EVOREL GEL (i.e. 1.5 mg) over a surface area of 400 cm2 of abdominal skin is followed by a progressive increase in estradiolaemia which reaches a mean peak of 40 pg/ml after a single administration.

Distribution

With repeated administration of the same dose over the same area, steady state is reached in 4 days. Average levels 24 hours after the last application are in the order of 40 pg/ml and the mean peak at the 22nd day is 70 pg/ml.

The bioavailability of percutaneous estradiol is dependent on the area of application and varies from one subject to another making it necessary to adapt the dosage to each individual case as a function of the clinical symptomatology.

When treatment is stopped, estradiol and urinary conjugated estradiol concentrations return to baseline in about 76 hours.

Metabolism

Estradiol is metabolised primarily in the liver to esterone by the P450 enzyme system, which has weak estrogenic activity. Estrone is either conjugated with glucuronic or supluric acids or reconverted to estradiol.

Due to the transdermal administration, there is no noticeable first pass effect.

Elimination

Estriol is the major urinary estradiol metabolite. However, glucuronic or supluric acids metabolites of estradiol and esterone are also found in the urine and bile.

Metabolites are excreted in bile undergone enterorhepatic recirculation or are excreted in the faeces.

5.3 Preclinical safety data

Acute toxicity of estrogens is low. Because of marked differences between animal species and between animals and humans preclinical results possess a limited predictive value for the application of estrogens in humans.

In experimental animals estradiol displayed an embryolethal effect already at relatively low doses; malformations of the urogenital tract and feminization of male fetuses were observed.

Preclinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenetic potential revealed estrogenic effects in relationship with the pharmacological activity of the molecule.

The finished product is a mild irritant for the skin, an irritant for the eyes, shows good tolerance with repeated topical administration and is non-sensitizing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96 per cent, Purified water, Propylene glycol, Diethylene glycol monoethyl ether (Transcutol), Carbomer (Carbopol 1382), Trolamine, Disodium edetate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not refrigerate or freeze .

6.5 Nature and contents of container

An aluminium bag placed in an opaque white polypropylene bottle containing 50 g of gel, with a dosing pump. Box of one or three bottles of 50g.

The pump delivers pushes of 0.5 g of gel corresponding to 0.5 mg of estradiol. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Theramex HQ UK Limited
5th Floor, 50 Broadway
London, SW1H 0BL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 49105 / 0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/03/2026

10 DATE OF REVISION OF THE TEXT

04/03/2026