Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Evorel 50 micrograms per 24 hours Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

3.2 mg estradiol hemihydrate per patch, releasing a nominal 50 micrograms (µg) estradiol per 24 hours.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

Evorel is a matrix type transdermal patch.

Description of Product
Patches are square with rounded corners and are 0.1 mm thick.Patches are made of a flat, two-layer laminate.The outer layer is a flexible, translucent and nearly colourless backing film.The inner layer is a monolayer adhesive film (matrix) composed of acrylic adhesive and guar gum, which contains the active ingredients.This adhesive layer is protected by a polyester foil release liner, which is removed prior to application of the patch to the skin.The polyester foil used is coated with silicone on both sides.It has an S-shaped incision to facilitate its removal prior to use.Each patch is individually enclosed in a protective, hermetically sealed, labelled pouch.

Evorel 50 is marked on the outer side with 'CE50' and has a surface area of 16 cm^2.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women.

Prevention of osteoporosis in postmenopausal 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

For treatment of post-menopausal symptoms, the lowest effective dose should be used.

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.

Adults

- *Treatment of oestrogen deficiency symptoms*

For women with an intact uterus, a progestogen must be added to Evorel for the prevention of adverse endometrial effects, e.g. hyperplasia and cancer. The regimen may be either cyclic or continuous sequential, that is, the progestogen is used for 12-14 consecutive days out of a cycle of 28 days. Only progestogens approved for addition to oestrogen treatment may be prescribed (e.g. oral norethisterone, 1mg/day or medroxyprogesterone acetate, 2.5mg/day).

Evorel 50 in conjunction with a progestogen (see above) can be initiated any time after the initial manifestation of oestrogen deficiency symptoms (e.g. hot flushes). Therapy should be started with Evorel 50.

The dose may be adjusted after the first month if necessary depending on efficacy and signs of over-oestrogenisation (e.g. breast tenderness). For maintenance therapy, the lowest effective dose should be used. A dose of 100µg of estradiol/24 hours should not be exceeded.

For hysterectomised women, Evorel can be initiated any time after the manifestation of oestrogen deficiency symptoms (e.g. hot flushes). Therapy should be started with Evorel 50. The dose may be adjusted after the first month if necessary depending on efficacy and signs of over-oestrogenisation (e.g. breast tenderness). For maintenance therapy, the lowest effective dose should be used. A dose of 100µg of estradiol/24 hours should not be exceeded.

The switch from another oestrogen-only therapy in post-menopausal women to Evorel may occur any time; the recommended starting dose is Evorel 50.

If there is a previous diagnosis of endometriosis, the addition of a progestogen to Evorel may also be considered for hysterectomised women.

- *Prevention of post-menopausal osteoporosis*

For women with an intact uterus therapy should be started with Evorel 50. Evorel 50 in conjunction with a progestogen (see above) can be initiated any time. The dose may be adjusted if necessary depending on signs of over-oestrogenisation (e.g. breast tenderness). Note, however, that the efficacy of Evorel 25 for the prevention of post-menopausal osteoporosis has not been demonstrated.

For hysterectomised women, therapy should be started with Evorel 50. The dose may be adjusted depending on efficacy and signs of over-oestrogenisation (e.g. breast tenderness). Note, however, that the efficacy of Evorel 25 for the prevention of post-menopausal osteoporosis has not been demonstrated. For maintenance therapy, the lowest effective dose should be used. A dose of 100µg of estradiol/24 hours should not be exceeded.

Switching from other HRT

Women on a continuous combined regimen wishing to switch from another oestrogen to Evorel may do so at any time. Women on a cyclic or continuous sequential regimen wishing to switch from another oestrogen to Evorel may do so at the end of a cycle of the current therapy.

Children

Evorel is not indicated in children.

Elderly

Data are insufficient in regard to the use of Evorel in the elderly (>65 years old).

Administration

Patches should be changed twice a week, i.e. every three to four days. Patches should be placed on a clean, dry, healthy, intact area of skin, on the trunk of the body below the waist. Creams, lotions or powders may interfere with the adhesive properties of the patch. The patch should not be applied on or near the breasts. The area of application should be changed, with an interval of at least one week allowed between applications to a particular site. The skin area selected should not be damaged or irritated. The waistline should not be used because excessive rubbing of the patch may occur.

The patch should be used immediately after opening the sachet. Remove one part of the protecting foil. Apply the exposed part of adhesive to the application site from the edge to the middle; avoid wrinkling of the patch. The second part of the protective foil should now be removed and the freshly exposed adhesive applied. Wrinkling should again be avoided and the palm of the hand used to press the patch onto the skin and to bring the patch to skin temperature at which the adhesive effect is optimised.

The patient should avoid contact between fingers and the adhesive part of the patch during application.

Should a patch fall off, a new patch should be applied immediately. However, the usual day of changing patches should be maintained. It is not necessary to remove the patch during bathing or showering. It is recommended, however, that the patch be removed prior to a sauna bath, and that a new patch is applied immediately thereafter. If a patch change is missed, the missed patch should be applied as soon as remembered. However, the usual day of changing patches should be maintained. Forgetting a dose may increase the likelihood of break-through bleeding or spotting.

To remove a patch, peel away an edge of the patch and pull smoothly away from the skin.

Any adhesive that remains on the skin after removal of the patch may be removed by washing with soap and water or rubbing it off with the fingers.

It is not necessary to remove the patch during bathing or showering.

Method of administration

Transdermal.

4.3 Contraindications

-Known, current or past or suspected breast cancer
-Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
-Undiagnosed genital bleeding
-Untreated endometrial hyperplasia
-Pregnancy or lactation
-Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism), thrombophlebitis
-Active or recent or past arterial thromboembolic disease (e.g. cerebrovascular accident, angina, myocardial infarction)
-Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
-Known thrombophilic disorders (eg. Protein C, Protein S, or antithrombin deficiency, see section 4.4)
-Known hypersensitivity to the active substances or to any of the excipients
-Porphyria.

4.4 Special warnings and precautions for use

- For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.
- Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more 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 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, 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. 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
- Mastopathy.

Reasons for immediate withdrawal of therapy:
Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy.

Endometrial hyperplasia and carcinoma

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see Section 4.8).The reported increase in endometrial cancer risk among oestrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment the 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 oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.Although progestogen treatment for at least 10 days per cycle reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer, 12-14 days per cycle is recommended to maximize endometrial protection. Such a sequential oestrogen/oestrogen-progestogen regimen results in cyclic bleeding in the majority of women.
- For women with a uterus who cannot tolerate or use a progestogen, unopposed oestrogen therapy can be considered but long-term monitoring is recommended, with endometrial surveillance, which may include biopsies, to be conducted annually or sooner if bleeding or spotting occurs.
- Evorel 75 and 100 are not recommended, as the endometrial safety of added progestogens have not been studied for transdermal doses of estradiol above 50 µg/day.
- Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.
- Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of a progestogen 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 cancerThe overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestogen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestogen therapy:

- The randomised placebo-controlled trial the 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 oestrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8). *Oestrogen-only therapy*:
- The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of oestrogen-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 oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer. Ovarian cancerOvarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined

oestrogen-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 a personal history or family history, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), pregnancy, post partum period, cancer and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.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.
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at a young age screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).However only a proportion of thrombophilic defects are identified by screening and patients should be offered counselling regarding its limitations. 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. 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.
- 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.

- 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 (eg, painful swelling of a leg, sudden pain in the chest, dyspnoea). Coronary artery disease (CAD)
- There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT. Oestrogen-onlyRandomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy. Combined oestrogen-progestogen therapyThe relative risk of CAD during use of combined oestrogen-progestogen HRT is slightly increased. The absolute risk of CAD is strongly dependent on age. The number of extra cases of CAD due to oestrogen-progestogen use is very low in healthy women close to menopause, but will rise with more advanced age. Ischaemic stroke
- Combined oestrogen-progestogen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8). Other conditions
- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- Oral oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).
- With transdermal administration, stimulation of the liver by the first-pass effect is avoided and thus, transdermally applied oestrogens might affect hormone binding proteins and other liver products less than oral hormones.
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should minimise exposure to the sun or ultraviolet radiation whilst taking HRT. Dementia
- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65. ALT elevations During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen

ombitasvir/paritaprevir/ritonavir with and without dasabuvir, 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, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. See section 4.5. Evorel is not to be used for contraception.Evorel should be kept away from children and pets.

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 barbiturates, phenylbutazone, meprobamate, anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and also bosentan.
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 (*Hypericumperforatum*) may induce the metabolism of oestrogens and progestogens.
Clinically, an increased metabolism of oestrogens may lead to decreased effect and changes in the uterine bleeding profile.
With transdermal administration, the first-pass effect in the liver is avoided and thus, transdermally applied oestrogens HRT might be less affected than oral hormones by enzyme inducers.

Effect of HRT with oestrogens on other medicinal products
Hormone contraceptives containing oestrogens 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 drugs together. Therefore, dose adjustment of lamotrigine may be necessary.

Pharmacodynamic interactions
During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, 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. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Evorel is not indicated during pregnancy. If pregnancy occurs during use of Evorel, treatment should be withdrawn immediately.

There are no clinical data on exposed pregnancies. Studies in animals have not shown reproductive toxicity.
The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of oestrogens and progestogens indicate no teratogenic or foetotoxic effect.

Lactation
Evorel is not indicated during lactation.

4.7 Effects on ability to drive and use machines

In normal use, Evorel would not be expected to have any effect on ability to drive or use machinery.

4.8 Undesirable effects

The safety of Evorel was evaluated in 2584 subjects who participated in 15 clinical trials and received at least one administration of Evorel. Subjects were also asked about application site signs and symptoms in 8 of the 15 clinical trials (N=1739 subjects). Based on safety data from these clinical trials, the most commonly reported (≥5% incidence) adverse drug reactions (ADRs) were (with % incidence): application site rash (20.8%), application site pruritus (19.8%), application site erythema (8.5%), headache (7.8%), and breast pain (6.6%).

Including the above-mentioned ADRs, the following table displays ADRs that have been reported with the use of Evorel from either clinical trial or post-marketing experiences. The displayed frequency categories use the following convention:

Very common (>1/10); common (>1/100 to <1/10); uncommon (>1/1,000 to <1/100); rare (>1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available clinical trial data).

Adverse Drug Reactions

Organ system class	**Very common (>1/10)**	**Common (≥1/100; <1/10)**	**Uncommon (≥1/1000; <1/100)**	**Rare (≥1/10,000; <1/1000)**	**Frequency not known**
Infections and Infestations			Genital candidiasis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Breast cancer*	Endometrial cancer
Immune System Disorders			Hypersensitivity		
Psychiatric disorders		Depressed mood			
Nervous system disorders		Migraine, Dizziness, Headache		Epilepsy	Cerebrovascular accident
Cardiac disorders			Palpitations		Myocardial infarction
Vascular disorders				Thrombosis	Deep vein thrombosis**
Respiratory, Thoracic and Mediastinal Disorders					Pulmonary embolism
Gastrointestinal disorders		Abdominal pain, Diarrhoea, Nausea	Flatulence	Abdominal distension	
Hepato-biliary disorders				Cholelithiasis	
Skin and subcutaneous tissue disorders		Pruritus, Rash			Angioedema
Musculoskeletal and Connective Tissue Disorders		Arthralgia	Myalgia		
Reproductive system and breast disorders		Breast pain, Metrorrhagia	Breast enlargement, Dysmenorrhoea		
General disorders and administration site conditions	Application site pruritus*, Application site rash*	Pain, Application site erythema*, Application site oedema*, Application site reaction	Oedema, Generalised oedema, Oedema peripheral		
Investigations		Weight increased			

*Additional adverse drug reactions reported in clinical trials of Evorel ® *(estradiol only)*.

The table below reports undesirable effects that have been reported in users of other hormone replacement therapy (HRT).

System Organ Class	**Common (≥1/100; <1/10)**	**Uncommon (≥1/1000; <1/100)**	**Rare (≥1/10,000; <1/1000)**
Metabolism and nutrition disorders	Weight decrease		
Psychiatric disorders			Anxiety,
			Libido decreased or Libido increased
Eye disorders		Visual disturbances	Contact lens intolerance
Gastrointestinal disorders	Nausea	Dyspepsia	Vomiting
Skin and subcutaneous tissue disorders		Erythema nodosum	Hirsutism
			Acne
Musculoskeletal and connective tissue disorders			Muscle cramps
Reproductive system and breast disorders		Breast tenderness	Premenstrual like syndrome
			Vaginal discharge
General disorders and administration conditions			Fatigue

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

Description of selected adverse reactions

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.
- The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).

- **Absolute risk estimates based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological study (MWS) 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/m^2)

Age at start HRT (years)	Incidence per 1 000 never-users of HRT over a 5 year-period (50-54 years)*	Risk ratio	Additional cases per 1 000 HRT users after 5 years
Oestrogen only HRT			
50	13.3	1.2	2.7
Combined oestrogen-progestogen			
50	13.3	1.6	8.0

*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m2)
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/m2)

Age at start HRT (years)	Additional cases 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
Oestrogen only HRT			
50	26.6	1.3	7.1
Combined oestrogen-progestogen			
50	26.6	1.8	20.8

*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m2)
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 year's use

Age range (years)	Incidenceper1000 women in placebo arm over 5years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5years (95% CI)
		CEE oestrogen-only	
50-79	21	0.8 (0.7-1.0)	-4 (-6-0)*
		CEE+MPA oestrogen & progestogens §	
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 5years of treatment :after 5years the risk was higher than in non-users.

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

Ovariancancer

Use of oestrogen-only or combined oestrogen-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
Oral oestrogen-only*			
50-59	7	1.2 (0.6 – 2.4)	1 (-3 – 10)
Oral combined oestrogen-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 oestrogen-progestogen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen + 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.*

The frequency of oestrogen-related adverse events (e.g. breast pain) is expected to increase with the dosage of estradiol transdermal systems.

The adverse event profile, their frequencies and severity in women with a uterus, treated with Evorel in conjunction with a progestogen, is expected to vary with the nature and the dose of the progestogen used concomitantly with Evorel.
Adverse events which have been reported in association with oestrogen/progestogen treatment are:

- **Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone HRT users than among non-users. For further information see Section 4.3 Contraindications and 4.4 Special warnings and precautions for use.

Other adverse reactions have been reported in association with oestrogen/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 website: www.hpra.ie

4.9 Overdose

By virtue of the mode of administration of Evorel, overdosage is unlikely, but effects can if necessary be reversed by removal of the patch. The most commonly observed symptoms of overdose with oestrogen therapy are breast pain or tenderness, nausea,

vomiting and break-through bleeding abdominal cramps or bloating. There is no specific antidote and treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03CA03
Estradiol hemihydrate
The active ingredient, estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy.

Clinical trial information
Relief of menopausal symptoms was achieved to a similar degree during the first few weeks of treatment with Evorel 50 and Evorel 100.

Prevention of osteoporosis

- Oestrogen deficiency at menopause is associated with increasing bone turnover and decline in bone mass.
- The effect of oestrogens on the bone mineral density (BMD) is dose-dependent; the relationship is not linear, however. Protection appears to be effective as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.
- Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestogen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/ or established osteoporosis, but the evidence for that is limited.
- In a clinical trial of two years duration comparing Evorel 50 and 100 to placebo, the increase in lumbar spine bone mineral density (BMD) with Evorel 50 was 4.46 ± 4.04 % (mean±SD). With Evorel 100, the gain in lumbar spine bone density was 5.93 ±4.34 %.
- The percentage of women who maintained or gained BMD in the lumbar spine with Evorel 50 was 84% and with Evorel 100, 92.5%.
- Evorel also had an effect on hip BMD. The increase in BMD in the femoral neck with Evorel 50 was 1.26 ± 2.86 % and with Evorel 100, 1.61±0.53 %. The percentage of women maintaining or gaining BMD in the femoral neck was 65 and 63.5 %, respectively. In the total hip, the increase in BMD was 2.17 ± 2.33 % with Evorel 50 and 2.82±0.51 % with Evorel 100. The percentage of women maintaining or gaining BMD in the total hip was 93 and 82.5 %, respectively.

5.2 Pharmacokinetic properties

The estradiol hemihydrate of the patch is taken up through the skin as estradiol. Estradiol is metabolised primarily in the liver to estrone, which has weak oestrogenic activity. Estrone is either conjugated with glucuronic or sulphuric acid or reconverted to estradiol. Conjugates are excreted mainly by the kidneys. In contrast to oral preparations, the estradiol/estrone ratio on use of Evorel is in the physiological range below 2, similar to that in pre-menopausal women. Estradiol circulates in the blood bound to sex hormone binding globulin (35-45%) and albumin (60-65%).

Estradiol is metabolised mainly in the liver by the P450 enzyme system. While the amounts of circulating estradiol/estrone are not considered clinically relevant modifiers of the activity of the P450 enzyme system, other drugs metabolised through the same pathway might inhibit or increase the metabolism of the hormones (see Section 4.5 Interactions).

Due to the transdermal administration, there is no noticeable first-pass effect. Pharmacokinetic parameters for Evorel 50 patches are shown in the following table.

Evorel 50
Serum estradiol (pmol/L; mean +/-SD)
C_{max} 277± 121 C_{96h} 113± 47 C_{avg} 173± 68

5.3 Preclinical safety data

Estradiol, which has been used in clinical practice worldwide for many years, is the subject of monographs in a number of major pharmacopoeias, has a well-established medicinal use and has recognised efficacy and an acceptable level of safety. Estradiol is the natural oestrogen in humans and animals. Preclinical effects were observed at exposures considered sufficiently in excess of the maximum human exposure, or were related to an exaggerated pharmacological effect, or were related to differences between species regarding hormonal regulation/metabolism and indicate little relevance to clinical use.

Subchronic skin irritation studies in rabbits and dermal sensitisation tests in guinea pigs have been performed.

The studies show that the estradiol transdermal patch is an irritant and that estradiol contributes to the irritancy. It is recognised that test studies on rabbits over-predict skin irritation which occurs in humans.

The dermal sensitisation test shows that Evorel is not a skin sensitiser.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adhesive acrylic polymer (Duro-Tak 387-2287)
Guar Gum (Meyprogat 90)
Hostaphan MN19 (Polyester film: removed before application)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25˚C.
Store within the original sachet and box.

6.5 Nature and contents of container

Each Evorel 50 patch is presented in a sealed protective sachet. The polyester film (Hostaphan MN19) is removed before application.
The sachets are packed in a cardboard carton, in packs of 8 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

Not applicable

7 MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited
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Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 10th June 2009

10 DATE OF REVISION OF THE TEXT

February 2024