SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Evorel Conti 50/170 micrograms per 24 hours Transdermal Patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch contains:

3.2 mg of estradiol hemihydrate equivalent to 3.1 mg estradiol
11.2 mg of norethisterone acetate equivalent to 9.82 mg norethisterone

Each patch releases a nominal 50 µg estradiol and 170 µg norethisterone acetate over 24 hours.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal Patch
Evorel Conti is a matrix type transdermal patch.

Description of the product
Each patch has an area of 16 cm2. Patches are square with rounded corners and are 0.1 mm thick. A patch is made of a flat, two-layer laminate. The outer layer is a flexible, translucent and nearly colourless backing film. It is marked on the outer side with "CEN1" in the centre of the lower edge. The inner layer is an 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 sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for the relief of menopausal symptoms in post-menopausal women more than 6 months post-menopause.

4.2 Posology and method of administration

Posology

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
Guidance on how to start therapy:
Post-menopausal women currently not on HRT may start Evorel Conti at any time.
Women on continuous sequential HRT wishing to switch to Evorel Conti may start Evorel Conti immediately after a cycle of the sequential HRT or after a hormone free period of two weeks. Starting Evorel Conti after a hormone free period may reduce the likelihood of uterine bleeding during the initial period of use of Evorel Conti. Evorel Conti patches should be worn continuously, without interruption. Patches should be applied to the trunk, below the waist. The patch should be changed twice a week, i.e. every three to four days. Application of a new patch should be to a site different from the previous application site.

If a patch detaches partially or completely prior to a scheduled change, it should be replaced immediately. 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. Wearing a patch by mistake for more than 4 days or any period without a patch may increase the likelihood of break-through bleeding or spotting.
It is not necessary to remove the patch during bathing or showering.

Paediatric population
Evorel Conti is not indicated in children.

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

Administration

Patches should be placed on a clean, dry area of skin on the trunk of the body below the waist. Creams, lotions, shower soaps, oils, liniments 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.

Patches 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. The palm of the hand should be used to press the patch onto the skin for approximately 30 seconds and to bring the patch to skin temperature at which the adhesive effect is optimised. Do not touch the adhesive part of the patch.

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

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

Method of administration

Transdermal use.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours (eg, 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 (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4)
- Known hypersensitivity to the active substances 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 re-instituting 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 contra-indications 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 Conti, in particular:
- Leiomyoma (uterine fibroids) or endometriosis
- 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 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

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. 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 risk may remain elevated for at least 10 years.
The addition of a progestogen for at least 12 days per month or continuous combined oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

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.

Breast cancer
The 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 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 cancer
Ovarian 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 recognized risk factors for VTE include a personal history or family history, use of oestrogens, older age, major surgery, prolonged immobilisation, severe obesity (BMI > 30 kg/m2) pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. 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, 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 young age or recurrent spontaneous abortion, screening may be offered after careful counselling regarding its limitations (only a 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.
Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration

should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, 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-only: Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.
Combined oestrogen-progestogen therapy: The 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).

Angioedema
Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

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.

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 radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-l-antitrypsin, ceruloplasmin). With transdermal administration, stimulation of the liver by the first-pass effect is avoided and thus, transdermally applied oestrogens and progestogens might affect hormone binding proteins and other liver products less than oral hormones.

Hypothyroidism
Patients who require thyroid hormone replacement therapy should have their thyroid function monitored regularly while on HRT to ensure that thyroid hormone levels remain in an acceptable range.

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 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/velpatasvir/voxilaprevir, 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, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin 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 following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. See section 4.5.

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.

Evorel Conti is not to be used as contraception.

The Evorel Conti patches 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, telaprevir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St. John's Wort (Hypericum perforatum) may induce the metabolism of oestrogens and progestogens.

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

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

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/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, 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, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin 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 following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

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.

Some laboratory tests may be influenced by oestrogen therapy, such as tests for glucose tolerance or thyroid function.

4.6 Fertility, pregnancy and lactation

Pregnancy
Evorel Conti is not indicated during pregnancy. If pregnancy occurs during use of Evorel Conti, treatment should be withdrawn immediately.
Clinically, data on a limited number of exposed pregnancies indicate no adverse effects of norethisterone acetate on the foetus. At doses higher than normally used in oral contraceptives and HRT formulations, masculinisation of female foetuses was observed.

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.

Breastfeeding
Evorel Conti is not indicated during breast feeding.

4.7 Effects on ability to drive and use machines

There are no known data on the effects of Evorel Conti on the ability to drive or use machinery.

4.8 Undesirable effects

The safety of Evorel Conti was evaluated in 196 subjects who participated in 3 clinical trials and received at least one administration of Evorel Conti. Based on safety data from these clinical trials, the most commonly reported (≥5% incidence) adverse drug reactions (ADRs) were (with % incidence): application site reaction (11.7%), menstrual disorder (7.1%), headache (8.2%), and breast pain (5.1%).

Including the above-mentioned ADRs, the following table displays ADRs that have been reported with the use of Evorel Conti from either clinical trial or post-marketing experiences, and additional ADRs that have been reported with the use of Evorel (estradiol alone) from clinical trial data. 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	-	-	Candidiasis	-	-
Neoplasms benign, malignant and unspecified (including cysts and polyps)	-	-	-	-	Breast noplasms**, Endometrial cancer**

Immune System Disorders	-	Hypersensitivity	-	-	-
Psychiatric disorders	-	Depression, Insomnia, Anxiety, Nervousness	Libido decreased	-	Mood swings
Nervous system disorders	-	Paraesthesia, Headache	Migraine	Epilepsy*	Cerebrovascular accident, Dizziness
Cardiac disorders	-	Palpitations	-	-	-
Vascular disorders	-	Hypertension, Varicose vein, Vasodilatation	-	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	-	Rash erythematous	Pruritus, Rash*	-	Stevens-Johnson syndrome
Musculoskeletal and Connective Tissue Disorders	-	Arthralgia, Back pain	Myalgia*	-	-
Reproductive system and breast disorders	-	Breast pain, Cervical polyp, Endometrial hyperplasia, Genital discharge, Dysmenorrhoea, Menorrhagia, Menstrual disorder, Metrorrhagia	-	-	Breast enlargement
General disorders and administration site conditions	Application site erythema, Application site pruritus, Application site rash, Application site reaction	Pain*, Oedema, Application site oedema*, Fatigue	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 combined hormone replacement therapy (HRT) by MedDRA system organ classes (MedDRA SOCs).

System Organ Class	**Very common (>1/10)**	**Common (≥1/100; <1/10)**	**Uncommon (≥1/1000; <1/100)**	**Rare (≥1/10,000; <1/1000)**	**Very rare (<1/10,000)**	**Frequency not known**
Psychiatric disorders	-	Affect lability	-	-	-	-
Nervous system disorders	-	-	Vertigo	-	-	-
Gastrointestinal disorders	-	Dyspepsia	Vomiting	-	-	-
Hepatobiliary disorders	-	-	-	Gallbladder disorder	Cholestatic jaundice	-
Skin and subcutaneous tissue disorders	-	Acne, Dry skin	Skin discolouration	-	-	Alopecia
Musculoskeletal and connective tissue disorders	-	Pain in extremity	-	Myasthenia	-	-
Reproductive system and breast disorders	Breast tenderness	Uterine spasms, Vaginal infection	-	Uterine leiomyoma, Fallopian tube cysts	-	-
Investigations	-	-	Transaminases increase	-	-	-

****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 substantially 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 range 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
		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 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/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-progestagen			
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)	Incidence per 1000 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 nouterus, 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 oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

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)).

Ovarian cancer
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:

WHISTUDIES-ADDITIONAL RISK OF VTE OVER 5 YEARS' USE

Age range(years)	Incidence per1000 women in place boarmover 5 years	Risk ratio &95 %CI	Additional cases per1000 HRTusers
Oral, oestrogen-only*			
50-59	**7**	**1.2(0.6-2.4)**	**1(-3-10)**
Oral combined, oestrogen-progesterone			
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 5YEARS' USE.

Age range(years)	Incidence per1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per1000 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.			

****Adverse events which have been reported in association with oestrogen/ progestogen treatment:

Venous thrombo-embolism, ie deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among HRT users than among non-users. For further information see Section 4.3 Contra-indications 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)
- Dry eyes
- Tear film composition changes

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

Signs and symptoms
Due to the mode of administration, overdose of oestradiol or norethisterone is unlikely to occur. Symptoms of overdose of oestrogen and progestogen therapy may include nausea, vomiting, break-through bleeding, breast tenderness, abdominal cramps and/or bloating. Over dosage of progestogens may lead to a depressive mood, fatigue, acne and hirsutism.

Treatment
These symptoms can be reversed by removing the Evorel Conti patch.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: GO3F A01

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. Estrogens prevent bone loss following menopause or ovariectomy.

Norethisterone:
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.

Clinical trial information:

Relief of oestrogen-deficiency symptoms and bleeding patterns:
- Relief of menopausal symptoms was achieved during the first few weeks of treatment.
- When starting Evorel Conti, bleeding episodes occur mostly during the first month of treatment, with a quick improvement of the bleeding profile. In first time users of HRT, or after a hormone free period of at least 2 weeks, absence of bleeding was seen in 33% of women during the first three months of treatment and 54% were bleed-free during months 2 and 3. When Evorel Conti was started directly after a cycle of sequential HRT, only 7.5% of the women were bleed-free during the first three months, 47% reported no bleeding for months 2 and 3. Over time, bleeding stops in the majority of women so that 63% of women from either group were bleed-free during the last 3 months of 12 months therapy with Evorel Conti. In women with well established menopause (mean 7 years since the last natural menstrual period), 56% were bleed-free during the first three months of treatment and 92% were bleed- free during months 10-12.
- Bleeding lasted five or less days in not more than 2 episodes per quarter year in >95% of subjects.

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 oestrone with weak estrogenic activity. Oestrone is either conjugated with glucuronic or sulphuric acid or reconverted to estradiol. Conjugates are excreted mainly through the kidneys. The estradiol/oestrone ratio on use of Evorel Conti is close to one, similar to pre-menopausal women.

Estradiol circulates in the blood bound to sex hormone binding globulin (35-45%) and albumin (60-65%). Norethisterone acetate is cleaved immediately on resorption to yield norethisterone. Norethisterone distributes widely in the body and circulates bound to sex hormone binding globulin (about 36%) and albumin (about 61%). It is metabolised mainly in the liver. Metabolites are conjugated with glucuronic or sulphuric acid. Conjugates are excreted in faeces and urine.

The hepatic metabolism of both estradiol and norethisterone is mediated primarily by the P450 enzyme system. While neither the amounts of circulating estradiol/oestrone nor of norethisterone after use of Evorel Conti are 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 with other medicinal products and other forms of interaction).

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

<u>Estradiol pharmacokinetics</u>
Following first use of an Evorel Conti patch by post-menopausal women, serum estradiol levels rise within 23 hours (T_{max}, single application) from, on average, -18 pmol/L (-5 pg/ml) by an average of 150 pmol/L (41 pg/mL) (C_{max}, single application). Levels decrease over 3.5 days to an average of 66 pmol/L (18 pg/mL). During continued use of Evorel Conti, estradiol levels rise over 21 hours from patch change (T_{max}, multiple application) by an average of 121 pmol/L (33 pg/mL) (C_{max}, multiple applications).
The 95% confidence interval for C_{max} ranges from 77 to 165 pmol/L (21 to 45 pg/mL). When patch use is discontinued, serum estradiol levels decrease with a half-life of 6.6 hours. After 24 hours, baseline levels are again observed.

<u>Norethisterone pharmacokinetics</u>
Following first use of Evorel Conti by post-menopausal women, serum norethisterone levels rise over 37 hours (T_{max}, single application) to 706 pmol/L (240 pg/mL) (C_{max}, single application) and then decrease to 420 pmol/L (143 pg/mL) at day 3.5. On patch change, levels rise again over 22 hours (T_{max}, multiple applications) to 756 pmol/L (257 pg/mL) (C_{max}, multiple applications). When patch use is discontinued, norethisterone levels decrease with a half-life of –15 hours.

5.3 Preclinical safety data

Estradiol and norethisterone acetate, which have been used in clinical practice worldwide for many years, are the subject of monographs in a number of major pharmacopoeias and have recognised efficacy and an acceptable level of safety. Estradiol is the natural estrogen 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.

Local tolerance studies with Evorel Conti were conducted in rabbits. In this model, Evorel Conti showed a mild irritation potential. It is recognised that the rabbit model is over-predictive of irritation of human skin.

Sensitisation studies with Evorel Conti in guinea pigs showed a weak sensitisation potential. Clinical trial experience with Evorel Conti use for up to two years gave no evidence of a clinically relevant sensitisation potential in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adhesive:
Acrylate-vinyl acetate copolymer (Duro-Tak 387-2287) Guar gum

Backing film:
Polyethylene terephthalate foil (Hostaphan MN19)

Release liner:
Siliconised polyethylene terephthalate foil (removed before application).

6.2 Incompatibilities

No creams, lotions, or powders should be applied to the skin area where the patch is to be applied to prevent interference with the adhesive properties of the patch.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original sachet and box.

6.5 Nature and contents of container

Each carton box has 8 patches in individual foil-lined sachets. The sachet comprises a 4-layer laminate including an aluminium humidity barrier and paper exterior surface.

6.6 Special precautions for disposal and other handling

Patches should be folded in half and disposed of in household waste (do not flush down the toilet).

7. MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited,
3rd Floor, Kilmore House,

Park Lane, Spencer Dock,
Dublin 1, D01YE64, Ireland

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