1. NAME OF THE MEDICINAL PRODUCT

EVOREL ® CONTI

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.

The Evorel Conti transdermal patch or Transdermal Delivery System (TDS), , is a flat two-layer laminate which is 0.1 mm in thickness. The first layer is a flexible, translucent, and nearly colourless backing film. The second layer is a monolayer adhesive film (matrix) composed of acrylic adhesive and guar gum and contains the hormones. This system is protected by a polyester foil release liner, which is affixed to the adhesive matrix and is removed prior to application of the patch to the skin. The polyester foil used is coated with silicone on both sides. The release liner has a S-shaped opening to facilitate its removal prior to use. Each TDS is enclosed in a protective, hermetically-sealed sachet.
Evorel Conti has a surface area of 16 sq cm and contains 3.2 mg of estradiol corresponding to a nominal release of 50 micrograms of estradiol per 24 hours and 11.2 mg of norethisterone acetate corresponding to a nominal release of 170 micrograms of norethisterone acetate per 24 hours. Each TDS is marked in the centre of the lower margin on the outside of the backing film: CEN1

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Hormone replacement therapy (HRT) for the relief of menopausal symptoms.

4.2 Posology and method of administration

Adults

Evorel Conti is a continuous combined HRT preparation.

Evorel Conti TDSs should be applied individually without interruption. TDSs should be applied twice weekly, every three to four days, to the trunk below the waist.

Insufficient data are available to guide dose adjustments for patients with severe liver or kidney function impairment.

For treatment of post- menopausal symptoms, the lowest effective dose should be used. HRT should be continued only as long as the benefit in alleviation of severe symptoms outweighs the risks of HRT.

Should a TDS fall off, it should be replaced immediately with a new patch. However, the usual day of changing TDSs should be maintained.

Method of Administration

The Evorel Conti TDS 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 TDS 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 TDS may occur.

The TDS 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 TDS. 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 TDS onto the skin and to bring the TDS to skin temperature at which the adhesive effect is optimized.

The patient should avoid contact between fingers and the adhesive part of the TDS 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.

Missed dose

If the patient forgets to change their patch, they should change it as soon as possible and apply the next one at the normal time. However, if it is almost time for the next patch, the patient should skip the missed one and go back to their regular schedule. Only one patch should be applied at a time.
Forgetting a dose may increase the likelihood of break-through bleeding and spotting.

To remove the Evorel Conti TDS, peel away an edge of the patch and pull smoothly away from the skin. (See Instructions for Use and Handling, Section 6.6.)

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

Children

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).

Route of administration

Transdermal use.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours (eg endometrial cancer) or pre-malignant tumours (e.g. untreated atypical endometrial hyperplasia)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thrombo-embolism (deep venous thrombosis, pulmonary embolism)
- Active or recent past arterial thrombo-embolic disease (e.g. cerebrovascular accident angina, myocardial infarction)
- Known thrombophilic conditions (e.g. protein C, protein S or antithrombin deficiency, see section 4.4)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Known hypersensitivity to the active 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 menopausal 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
- A history of, or risk factors for, thrombo-embolic 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

Conditions which require monitoring while on oestrogen therapy:

- Oestrogens may cause fluid retention. Cardiac or renal dysfunction should be carefully observed
- Disturbances or mild impairment of liver function
- History of cholestatic jaundice
- Pre-existing hypertriglyceridaemia. Rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition

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. 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 for 12-14 days per cycle 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 thrombo-embolism

HRT is associated with a 1.3-3 fold risk of developing venous thrombo-embolism (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, major surgery, prolonged immobilisation, severe obesity (BMI > 30 kg/m^2), use of oestrogens, older age, 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.

The 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 thrombo-embolic symptom (eg, painful swelling of a leg, sudden pain in the chest, dyspnoea).

Smoking

Smoking is a risk factor of VTE. Women should be advised not to smoke if they wish to use Evorel Conti.

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).

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.

Angioedema

Oestrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary 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.

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

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).

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.

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 for contraception. Women of child-bearing potential should be advised to use non-hormonal contraceptive methods to avoid pregnancy.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine) 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 raise 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 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).

Oestrogen-containing oral contraceptives 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 estrogen-containing 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.

Data on a limited number of exposed pregnancies indicate adverse effects of norethisterone on the foetus. At doses higher than normally used in oral contraceptives and HRT formulations, masculinisation of female foetuses was observed.

The results of most epidemiological studies to date, relevant to inadvertent foetal exposure to combinations of oestrogens and progestogens indicate no teratogenic or foetotoxic effect.

Breast Feeding

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

Infections and Infestations	
Uncommon	Candidiasis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Frequency not known	Breast neoplasms, Endometrial cancer
Immune System Disorders	
Common	Hypersensitivity
Psychiatric disorders	
Common	Depression, Insomnia, Anxiety, Nervousness
Uncommon	Libido decreased
Frequency not known	Mood swings
Nervous system disorders	
Common	Paraesthesia, Headache
Uncommon	Migraine
Rare	Epilepsy*
Frequency not known	Cerebrovascular accident, Dizziness
Cardiac disorders	
Common	Palpitations
Vascular disorders	
Common	Hypertension, Varicose vein, Vasodilatation
Rare	Thrombosis*
Frequency not known	Deep vein thrombosis,
Respiratory, Thoracic and Mediastinal Disorders	
Frequency not known	Pulmonary embolism
Gastrointestinal disorders	
Common	Abdominal pain, Diarrhoea*, Nausea
Uncommon	Flatulence*

Frequency not known	Abdominal distension
Hepato-biliary disorders	
Frequency not known	Cholelithiasis
Skin and subcutaneous tissue disorders	
Common	Rash erythematous
Uncommon	Pruritus, Rash*,
Frequency not known	Stevens-Johnson syndrome
Musculoskeletal and Connective Tissue Disorders	
Common	Arthralgia, Back pain
Uncommon	Myalgia*
Reproductive system and breast disorders	
Common	Breast pain, Cervical polyp, Endometrial hyperplasia, Genital discharge, Dysmenorrhoea, Menorrhagia, Menstrual disorder, Metrorrhagia
Frequency not known	Breast enlargement
General disorders and administration site conditions	
Very Common	Application site erythema, Application site pruritus, Application site rash, Application site reaction
Common	Pain*, Oedema, Application site oedema* Fatigue
Uncommon	Generalised oedema, Oedema peripheral*,
Investigations	
Common	Weight increased

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

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

Psychiatric disorders	
Common	Affect lability
Nervous system disorders	
Uncommon	Vertigo
Gastrointestinal disorders	
Common	Dyspepsia
Uncommon	Vomiting
Hepatobiliary disorders	
Rare	Gallbladder disorder,
Very rare	Cholestatic jaundice
Skin and subcutaneous tissue	
Common	Acne, Dry skin
Uncommon	Skin discolouration
Frequency not known	Alopecia
Musculoskeletal and connective tissue disorders	
Common	Pain in extremity

Rare	Myasthenia
Reproductive system and breast disorders	
Very Common	Breast tenderness
Common	Uterine spasms, Vaginal infection
Rare	Uterine leiomyoma, Fallopian tube cysts,
Investigations	
Uncommon	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 estimations based on results of the largest randomised 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/m^2)

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
		Oestrogen only HRT	
50	13.3	1.2	2.7
		Combined oestrogen-progestagen	
50	13.3	1.6	8.0

*Taken from baseline incidence rates in England in 2015 in 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 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 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95% CI)
		CEE oestrogen only	
50-79	21	0.8 (0.7-1.0)	-4 (-6 - 0)* ‡
		CEE + MPA oestrogen & progestagens ‡	
50-79	17	1.2 (1.0-1.5)	+4 (0 - 9)

‡ 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.
* WHI study in women with no uterus, which did not show an increase of breast cancer.

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:

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 & 95%CI**	**Additional cases per 1000 HRT users**
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 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**
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 hormone 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://sideeffects.health.gov.il

4.9 Overdose

Signs and symptoms

Due to the mode of administration, overdose of oestradiol or norethisterone is unlikely to occur. Symptoms of overdose with oral oestrogens are breast tenderness, nausea, vomiting and/or metrorrhagia. 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: G03F A01

Estradiol hemihydrate:

The active ingredient, synthetic 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.

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 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 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.

Starting Evorel Conti after a hormone free period may reduce the likelihood of uterine bleeding during the initial period of use of Evorel Conti.

In three clinical trials of one year duration, uterine bleeding episodes were reported as an adverse event by 53 of 344 (16%) women - the most frequently reported undesirable effect.

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. 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.

After one year of treatment with Evorel Conti, the increase in lumbar spine bone mineral density (BMD) was 2.94 ± 2.62 % (mean±SD). The percentage of women who maintained or gained BMD in the lumbar zone during treatment was 90%.

Evorel Conti also had an effect on hip BMD. The increase in BMD in the femoral neck was 2.42 ± 3.04 % and the percentage of women maintaining or gaining BMD in the femoral neck was 82%. In the total hip, the increase in BMD was 1.73 ± 2.55 % (mean±SD) with 74% women maintaining or gaining in BMD.

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 estrogenic activity. Estrone is either conjugated with glucuronic or sulphuric acid or reconverted to estradiol. Conjugates are excreted mainly by the kidneys. The estradiol / estrone 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 sulfuric acid. Conjugates are excreted in faeces and urine.

The hepatic metabolism of both estradiol and norethisterone is mediated primarily by the P450 enzyme system. (see Section 4.5, Interactions with other medicinal products and other forms of interaction).

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

Estradiol pharmacokinetics

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.

Norethisterone pharmacokinetics

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

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.

Norethisterone, like other progestogens, caused virilisation of female foetuses in rats and monkeys. After high doses of norethisterone embryolethal effects were observed.

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: Duro-Tak (acrylate-vinylacetate copolymer)

Guar gum

Backing film: Hostaphan MN 19 (polyethylene terephthalate foil).

Release liner: siliconised polyethylene terephthalate foil, is removed before application.

6.2 Incompatibilities

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

6.3 Shelf Life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25^0C, within the original sachet and box.

Keep out of reach of children. This also applies to used and disposed TDSs.

6.5 Nature and content of container

Each carton box has 8 TDSs in individual foil-lined sachets. The sachet comprises a 4 layer laminate including:

-surlyn-ionomer film on the inside

- then aluminium foil

- then polyethylene

- with a layer of bleached reinforced paper on the outside

6.6 Special precautions for disposal

The EVOREL CONTI TDS should be placed on a clean, dry area of skin on the trunk of the body below the waist. Creams, lotions, or powders may interfere with the adhesive properties of the EVOREL CONTI TDS. The TDS should not be applied on or near to 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 TDS may occur.

The TDS 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 TDS. 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 TDS onto the skin and to bring the TDS to skin temperature, at which the adhesive effect is optimised. Do not touch the adhesive part of the TDS.

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

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

The TDSs should be disposed of in household waste (do not flush down the toilet).

7. MANUFACTURER

Theramex Ireland Limited, 3RD Floor, Kilmore House, Park Lane, Spencer Dock, Dublin D01 YE64, Ireland

8. REGISTRATION HOLDER

Truemed Ltd, Israel, 10 Beni Gaon St., Poleg Inductrial Park, P.O.Box 8105, Netanya 4250499.

9. REGISTRATION NUMBER

121-50-29726

Revised in June 2022 according to Ministry of Health guidelines

PI-1049 03-06.22