## 1. Name of the medicinal product

Evorel® 50

## 2. Qualitative and quantitative composition

3.2 mg of estradiol (as hemihydrate) /patch

## 3. Pharmaceutical form

Transdermal patch

EVOREL is a square shaped, transparent, self-adhesive transdermal delivery system (patch) of 0.2 mm thickness for application to the skin surface.

It consists of a monolayered adhesive matrix throughout which 17β estradiol is uniformly distributed. The adhesive matrix is protected on the outside surface (from clothes etc) by a polyethylene teraphthalate backing foil, while the adhesive surface of the patch is covered by a polyester sheet (the release liner) which is removed before placing the patch on the body surface. This release liner has an S-shaped incision which facilitates easy removal from the patch.

EVOREL 50 is marked 'CE50', has a surface area of 16 sq. cm and contains 3.2 mg estradiol

(as hemihydrate) corresponding to a release rate of 50 micrograms of estradiol in 24 hours.

## 4. Clinical particulars

### 4.1 Therapeutic indications

Deficiency symptoms by absence of Estrogen after the menopause or after surgical removal of the ovarians. They comprise hot flushes, insomnia, atrophies of the urogenital system, changes of mood and increasing loss of the bone substance, which can lead to osteoporosis. In women with intact uterus, estrogen substitution must always be supplemented with a sequential gestagen therapy.

### 4.2 Posology and method of administration

***Adults***

Evorel is an oestrogen-only HRT patch applied to the skin twice weekly.

For initiation and continuation of treatment of menopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used.

For women with an intact uterus progestogen should normally 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.

Only progestogens approved for addition to oestrogen treatment may be prescribed (e.g. oral norethisterone, 1mg/day or medroxyprogesterone acetate, 2.5mg/day) and should be added for at least 12-14 days every month/28 day cycle.

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

***Treatment of oestrogen deficiency symptoms***

Therapy should be started with one Evorel 50 patch (delivering 50 micrograms of estradiol/24 hours) and the dose 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; For woman with a uterus, doses of oestradiol above 50 µg/day have not been studied and are therefore not recommended. For women without a uterus, a maximum dose of 100 micrograms of estradiol/24 hours should not be exceeded.

**Guidance on how to start therapy:**

Post-menopausal women currently not on HRT may start Evorel at any time.

***Switching from other HRT***

The switch from another oestrogen-only therapy in post-menopausal women to Evorel may occur at any time.

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 a sequential combined HRT preparation to Evorel may do so at the end of a cycle of the current therapy or after a 7 days hormone free interval.

***Method of Administration***

The EVOREL transdermal delivery system (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. **Evorel 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.

To remove a patch, 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 the patch may be removed by washing with soap and water or rubbing it off with the fingers or use baby oil.

***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.

There is an increased likelihood of break-through bleeding and spotting when a patch is not replaced at the normal time.

***Children***

Evorel is not indicated in children.

***Elderly***

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

***Route of administration***

Transdermal use.

## 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
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency see section 4.4);
- Active or recent past arterial thrombo-embolic 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 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 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
- 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
- Hereditary angioedema
- 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 cyclically for at least 12 days per months/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.
- For oral doses of estradiol >2mg, conjugated equine oestrogens >0.625 mg and patches >50 ug/day the endometrial safety of added progestagens has not been demonstrated.

- Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

*Oestrogen-only therapy*

From 1 to 5 years in women with a uterus has been estimated to increase the risk of endometrial cancer 3-fold (from a baseline lifetime risk of about 3% for a woman aged 50 years), with effects persisting for several years after oestrogen is stopped. The addition of a progestogen for 12-14 days per cycle or continuous combined oestrogen/progestogen therapy in non-hysterectomised women greatly reduces this risk.

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 maximise endometrial protection. Such a sequential oestrogen/oestrogen-progestogen regimen results in cyclic bleeding in the majority of women.

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 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 higher relative risk of developing venous thrombo-embolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users, it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged 60-69 years. It is estimated that in healthy women who use combined oral HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8).

- 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). Personal or strong family history of thrombo-embolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated.
- Generally recognised risk factors for VTE include a personal history or family history, use of oestrogens, older age, severe obesity (BMI > 30 kg/m2), pregnancy/postpartum 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, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only 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.
- 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 thrombo-embolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnoea).
- Smoking is a risk factor of VTE. Women should be advised not to smoke if they wish to use Evorel.

**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-progestagen 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**

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

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 or duration of use. 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 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 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 unchanged. 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).

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.

**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.

**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.

Evorel 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 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, transdermal 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).

Estrogen-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.

At 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.

## 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 the 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

| | |
|---|---|
| **Infections and Infestations** | |
| Uncommon | Genital candidiasis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | |
| Rare | Breast cancer |
| Frequency not known | Endometrial cancer |
| **Immune System Disorders** | |
| Uncommon | Hypersensitivity |
| **Psychiatric disorders** | |
| Common | Depressed mood |
| **Nervous system disorders** | |
| Common | Migraine, Dizziness, Headache |
| Rare | Epilepsy |
| Frequency not known | Cerebrovascular accident |
| **Cardiac disorders** | |
| Uncommon | Palpitations |
| Frequency not known | Myocardial infarction |
| **Vascular disorders** | |
| | |

| | |
|---|---|
| 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 |
| Rare | Abdominal distension |
| **Hepato-biliary disorders** | |
| Rare | Cholelithiasis |
| **Skin and subcutaneous tissue disorders** | |
| Common | Pruritus, Rash |
| Frequency not known | Angioedema |
| **Musculoskeletal and Connective Tissue Disorders** | |
| Common | Arthralgia |
| Uncommon | Myalgia |
| **Reproductive system and breast disorders** | |
| Common | Breast pain, Metrorrhagia |
| Uncommon | Breast enlargement, Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very Common | Application site pruritus*, Application site rash* |
| Common | Pain, Application site erythema*, Application site oedema*, Application site reaction |
| Uncommon | Oedema, 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).

| | |
|---|---|
| **Metabolism and nutrition disorders** | |
| Common | Weight decrease |
| **Psychiatric disorders** | |
| Rare | Anxiety, Libido decreased, Libido increased |
| **Eye disorders** | |
| Uncommon | Visual disturbances |
| Rare | Contact lens intolerance |
| **Gastrointestinal ɒdisorders** | |
| Common | Nausea |
| Uncommon | Dyspepsia |
| Rare | Vomiting |
| **Skin and subcutaneous tissue** | |
| Uncommon | Erythema nodosum, |
| Rare | Hirsutism, Acne |
| **Musculoskeletal and connective tissue disorders** | |
| Rare | Muscle cramps |
| **Reproductive system and breast disorders** | |
| Uncommon | Breast tenderness |
| Rare | Vaginal discharge, Premenstrual like syndrome |
| **General disorders and administration conditions** | |
| Rare | Fatigue |

Other adverse reactions have been reported in association with oestrogen/progestogen treatment:

- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme,
- Vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).

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

**Breast Cancer risk**

An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.

The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestagen 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 below:

**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 (95% CI) |
|---|---|---|---|
| | | **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 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 differs by EU country, the number of additional cases of breast cancer will also change proportionately.

**<u>Estimated</u> 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) |

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

§ When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

## Endometrial Cancer risk

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2- to 12-fold greater compared with non- users. Adding a progestogen to oestrogen-only therapy greatly reduces 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.

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

Venous thrombo-embolism, 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 Contra-indications and 4.4 Special warnings and precautions for use.

**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*** | | | |
| 50-79 | 7 | 1.2 (0.6-2.4) | 1 (-3 - 10) |
| **Oral combined oestrogen-progestogen** | | | |
| 50-79 | 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-progestagen HRT over the age of 60 (see section 4.4).

**Risk of ischaemic stroke**

• The use of oestrogen-only and oestrogen + progestagen 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) |

**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 https://sideeffects.health.gov.il

## 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 breakthrough 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, 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.

*Clinical trial information:*

− *Relief of oestrogen-deficiency symptoms and bleeding patterns*

- Relief of menopausal symptoms was achieved to a similar degree during the first few weeks of treatment.

- *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 estrogenic 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. (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.

| | Serum estradiol (pmol/L; mean+/-SD) |
|---|---|
| Cmax | 277± 121 |
| C96h | 113± 47 |
| Cavg | 173± 68 |

### 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.

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

Duro-Tak (acrylate vinylacetate copolymer)

Guar gum (meyprogat)

Hostaphan MN19 (polyethylene terepahtalate foil-removed before application)

### 6.2 Incompatibilities

None known

### 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°C.

Evorel should be kept away from children and pets.

### 6.5 Nature and contents of container

Each Evorel patch size is presented in a sealed protective pouch. The pouches are packed in a cardboard carton.

### 6.6 Special precautions for disposal and other handling

None.

## 7. Manufacturer:

Theramex Ireland Limited, Ireland

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

**8. Registration Holder:**

Truemed Ltd, Israel

10 Beni Gaon St., Poleg Industrial Park, P.O.Box 8105, Netanya 4250499.

**9. Registration number**

103-09-28671

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