**PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**
Schedule 4

**PROPRIETARY NAME AND DOSAGE FORM**
**EVOREL® SEQUI** patch

**COMPOSITION**
**EVOREL SEQUI** is a combination of an oestradiol matrix type transdermal patch and an oestradiol/norethisterone acetate matrix type transdermal patch (sequential regimen).

**EVOREL SEQUI** is a transdermal therapy comprising:
(a) 4 **EVOREL 50**, each containing 3,1 mg oestradiol, formulated as 3,2 mg of oestradiol hemihydrate. Each **EVOREL 50** patch delivers 50 µg of oestradiol per 24 hours.
(b) 4 **EVOREL CONTI** each containing 3,1 mg oestradiol formulated as 3,2 mg of oestradiol hemihydrate and 9,82 mg norethisterone, formulated as 11,2 mg of norethisterone acetate. Each **EVOREL CONTI** delivers 50 µg of oestradiol and 170 µg of norethisterone acetate per 24 hours.

The following are the inactive ingredients of **EVOREL SEQUI, EVOREL 50** and **EVOREL CONTI**:
- Adhesive: acrylate-vinylacetate copolymer
- Guar gum
- Backing film: polyethylene terephathalate foil
- Release liner: siliconised polyethylene terephathalate foil is removed before application

**EVOREL SEQUI** contains no sugar.

**PHARMACOLOGICAL CLASSIFICATION**
A 21.8.1 Oestrogens (**EVOREL 50**)
A 21.8.2 Progesterones with oestrogens (**EVOREL CONTI**)

**PHARMACOLOGICAL ACTION**
**Pharmacodynamic properties**
**Oestradiol ($E_2$)**
The active hormone of **EVOREL SEQUI** is 17β-oestradiol a biologically oestrogen produced by the ovary.

**Norethisterone acetate (NETA)**
Norethisterone acetate, used in the **EVOREL CONTI** of **EVOREL SEQUI**, is hydrolysed to norethisterone, a synthetic 19-nortestosterone derivative of the 13-methyl gonane group with potent progestational activity. Transdermal norethisterone acetate administration prevents oestrogen-related endometrial proliferation.

**Pharmacokinetic Properties**
**Oestradiol**
Oestradiol distributes widely in the body tissues and is bound to albumin (about 60 – 65 %) and sex-hormone-binding globulin (about 35 – 45 %) in serum. Serum protein-binding fractions remain unaltered following transdermal delivery of oestradiol.

Oestradiol is promptly eliminated from the systemic circulation. Oestradiol is metabolised principally into the less pharmacologically active oestrone and its conjugates.
Oestradiol, oestrone and oestrone sulphate are interconverted to each other and are excreted in urine as glucuronides and sulphates. The skin metabolises oestradiol only to a small extent.

**Norethisterone**
Norethisterone acetate is hydrolysed to the active progestagen, norethisterone. Transdermal delivery of norethisterone acetate produces a sustained and effective level of norethisterone in the systemic circulation.
Norethisterone distributes widely in the body tissues and is bound to albumin (about 61 %) and sex-hormone-binding globulin (about 36 %) in serum. Norethisterone is primarily metabolised by the liver by reduction of the α, β-unsaturated ketone structure in ring A of the molecule.
Among the four possible stereoisomeric tetrahydrosteroids, the 5ß-, 3α-hydroxy-derivative appears to be the predominant metabolite. These compounds are primarily excreted in urine and faeces as sulphates and glucuronide conjugates.

**$E_2$/NETA combination**
**Oestradiol:** In a single and multiple application study in postmenopausal women, serum oestradiol concentrations increased rapidly from pre-treatment levels (about 5 pg/ml) after application of **EVOREL CONTI**.
At four hours after application, the mean serum oestradiol concentration was about about 19 pg/ml.

A mean peak serum oestradiol concentration of about 41 pg/ml above the pre-treatment level was observed at about 23 hours following application. Serum oestradiol concentrations remained elevated for the 3,5-day application period. Concentrations returned rapidly to pre-treatment levels within 24 hours following removal of the patch. A serum half-life of about 6,6 hours was determined following removal of the patch.
Multiple applications of the **EVOREL CONTI** resulted in little or no accumulation of oestradiol in the systemic circulation. Higher circulating levels of oestradiol were attained from **EVOREL 50**. Both formulations were shown to achieve serum oestradiol concentration typically seen in pre-menopausal women.
During use of **EVOREL CONTI** the mean serum oestradiol to oestrone ($E_2/E_1$) ratios increased rapidly and were maintained at physiological levels at approximated 1. The $E_2/E_1$ ratios returned to pre-treatment levels within 24 hours after removal of the patch. An average $E_2/E_1$ ratio that approximated 1 was also maintained over an entire 3,5-day application period following **EVOREL 50** application.

**Norethisterone:** In a single and multiple application study in postmenopausal women, serum norethisterone concentrations rose within 1 day after application of an **EVOREL CONTI** to a mean steady state level of about 199 pg/ml. Mean steady state serum norethisterone concentrations ranging between about 141 - 224 pg/ml were maintained for the entire 3,5-day application period following multiple applications.
Mean concentrations declined rapidly to the lower limit of assay quantitation at 24 hours after removal of the patch. A serum half-life of about 15 hours was determined following removal of the patch; indicative of the skin depot effect.

As expected from the transdermal delivery only a transient and limited increase in serum norethisterone concentration was observed following multiple applications of the patch.

**INDICATIONS**
Hormone replacement therapy [HRT] for the relief of menopausal symptoms (vasomotor symptoms such as hot flushes and atrophic vaginitis/vulvitis) for women with an intact uterus.

**CONTRAINDICATIONS**
- Known hypersensitivity to oestradiol, norethisterone acetate or any other component of this product
- Known current, past or suspected breast cancer.
- Family history of breast cancer.
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer) or pre-malignant tumours (e.g. untreated atypical endometrial hyperplasia).
- Undiagnosed genital bleeding.
- Pregnancy and lactation. (*see **PREGNANCY and LACTATION***)
- Active liver disease, or a history of liver disease as long as liver function tests have failed to return to normal.
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism).
- Known thrombophilic conditions.
- Inherited thrombophilia.
- Active or recent past arterial thromboembolic disease (e.g. cerebrovascular accident, myocardial infarction).
- Porphyria
- Patients known with inherited genetic mutations: BRCA1 and BRCA 2 genes.
- Early menstrual periods (before age 12 years).
- History of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma in situ).
- Previous treatment using radiation therapy to the chest or breast.
- Previous treatment with diethylstilboestrol (DES).
- Depression not well controlled with treatment.
- A history of depression with the use of oestrogen and/or progesterone/ progestogen containing medicines irrespective of the indication, dosage formulation and route of administration.

**WARNINGS AND SPECIAL PRECAUTIONS**
Prior to commencing, and periodically during, it is recommended that the patient be given a thorough physical and gynaecological examination. A complete medical and family history of thrombophlebitis or thromboembolic disorders should be taken. Repeated breakthrough bleeding, unexplained vaginal bleeding, and changes noticed during breast examination require further evaluation.
A careful appraisal of the risk/benefit ratio should be undertaken before the initiation of treatment.

**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 SEQUI** in particular:

- Leiomyoma (uterine fibroids) or endometriosis.
- Risk factors for thromboembolic disorders (see below).
- Risk factors for oestrogen dependent tumours, e.g. first degree relative with breast cancer.
- Hypertension.
- Liver disorders.
- Diabetes mellitus.
- Cholelithiasis.
- Migraine or severe headache.
- Systemic lupus erythematosus.
- A history of endometrial hyperplasia (see below)
- Epilepsy.
- Mastopathy.

**Conditions which require monitoring while on EVOREL SEQUI therapy:**
- Oestrogens such as in **EVOREL SEQUI** may cause fluid retention.
- Cardiac or renal dysfunction should be carefully observed.
- Disturbances of liver function.
- History of cholestatic jaundice.
- Pre-existing hypertriglyceridaemia. Cases of large increases of plasma triglycerides leading to pancreatitis have been reported in this condition.

**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.
- Increase in blood pressure.
- New onset of migraine-type headache.
- Pregnancy.

**Breast cancer**
**EVOREL SEQUI** contains oestrogen only which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55 575 women 40 – 59 years of age who used menopausal hormone therapy (MHT).
The risk increased steadily with duration of use and was slightly greater for oestrogen-progestogen than oestrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment.
The relative risk (RR) to develop breast cancer for oestrogen-progestogen preparations was 1,60 at 1 – 4 years and RR = 2,08 at 5 – 14 years, while that for oestrogen only preparations was 1,17 at 1 – 4 years and 1,33 at 5 – 14 years. There was no risk to develop breast cancer in women who started MHT at 60 years of age.
All women on **EVOREL SEQUI** should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. Mammography evaluations should be done on patient age, risk factors and prior mammogram results.

*Combined oestrogen-progestagen therapy:*
The randomised placebo-controlled trial the (Women's Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years.

*Oestrogen-only therapy:*
The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT.
The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment. HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

**Ovarian Cancer**
Long-term (at least 5 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies.
Some studies including the WHI trial suggest that the long-term use of combined HRTs such as in **EVOREL SEQUI** may also confer an increased risk.

**Venous thromboembolism**
Hormone replacement therapy [HRT] is associated with a higher relative risk of developing venous thromboembolism (VTE), such as 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.
Personal or a strong family history of recurrent thromboembolism or recurrent spontaneous abortions should be investigated in order to exclude a thrombophilic predisposition.
Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment is initiated, the use of **EVOREL SEQUI** in such patients should be viewed as contraindicated.
Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of **EVOREL SEQUI**.
The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or surgery. Scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery**, EVOREL SEQUI** treatment should be discontinued four to six weeks and earlier if possible ahead of surgery.
Treatment should not be restarted until after the woman is completely mobilized.

If VTE develops after initiating therapy**, EVOREL SEQUI** should be discontinued. Patients should be told to contact their doctors immediately when they become aware of a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnoea).

**Coronary artery disease (CAD)**
*Oestrogen-only:*
Randomised controlled studies found no protective effect in hysterectomised women using oestrogen-only therapy for the risk of CAD.

*Combined oestrogen-progestagen* therapy such as **EVOREL SEQUI**:
The relative risk of CAD during use of combined oestrogen-progestagen HRT is increased. -

**Stroke**
There is an increased risk of stroke in healthy women during treatment with HRT. Combined oestrogen-progestagen and oestrogen-only therapy are associated with an increased in risk of ischaemic stroke.

**Dementia**
HRT use does not improve cognitive function. There is evidence of increased risk of dementia in women using continuous combined HRT such as **EVOREL SEQUI** or oestrogen-only HRT.

**Depressed mood, depression and the risk of suicidality**
Mood changes and depression are side effects reported with the use of hormonal containing products including **EVOREL SEQUI**. There is some evidence that use of oestrogen and/or progesterone/progestogen containing medicines may be associated with severe depression and a higher risk of suicidal thoughts/behavior (e.g. talking about suicide, withdrawing from social contact, having mood swings, being preoccupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment with **EVOREL SEQUI**.

**Other conditions**
Concomitant administration of lamotrigine with medicines containing both ethinyl oestradiol and a progestagen, such as **EVOREL SEQUI**, increases the risk of seizures in epileptic patients (*See **INTERACTIONS***).

**EVOREL SEQUI** is not to be used as contraception.
**EVOREL SEQUI** should be kept away from children.

**INTERACTIONS**
Medicines, which induce microsomal liver enzyme activity, may alter oestrogen and progestogen metabolism and reduce the therapeutic effect of **EVOREL SEQUI**. Examples of such medicines are barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone, rifampicin, rifabutin, bosentan and certain non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine and efavirenz) used in the treatment of HIV/AIDs infections.

Ritonavir and nelfinavir, although known as strong inhibitors of the cytochrome P450 isoenzymes, by contrast exhibit inducing properties when used concomitantly with steroid hormones.
Metabolism may be affected by St. John's wort preparations (*Hypericum perforatum*), which induce certain cytochrome P450 isoenzymes in the liver (e.g. CYP 3A4) as well as P-glycoprotein.
The induction of the P450 isoenzymes may reduce plasma concentrations of the oestrogen component of **EVOREL SEQUI** possibly resulting in a decrease in therapeutic effects and increased vaginal bleeding.

The induction of these same isoenzymes may also reduce circulating concentrations of the progestin component of **EVOREL SEQUI** which could result in a diminished effect against oestrogen-induced endometrial hyperplasia.
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 **EVOREL SEQUI** 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 medicines together. Therefore, dosage adjustment of lamotrigine may be necessary (*See **WARNINGS and SPECIAL PRECAUTIONS***).

**PREGNANCY AND LACTATION**
The use of **EVOREL SEQUI** is contraindicated in pregnancy or lactation.
If pregnancy occurs during medication with **EVOREL SEQUI**, treatment should be withdrawn immediately.

**DOSAGE AND DIRECTIONS FOR USE**
**Dosage**
*ADULTS*:

**EVOREL 50** and **EVOREL CONTI** should be applied individually in the following sequence: four **EVOREL 50** followed by four **EVOREL CONTI**. The cycle should be repeated without interruption. Patches 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.

**EVOREL SEQUI** should not be continued for longer than 5 years.
It is important that the patch be used in the correct sequence to ensure regular cyclic bleeding. Most patients will experience vaginal bleeding after the start of the progestagen therapy.
Should a patch fall off, it should be replaced immediately with a new equivalent **EVOREL 50** or **EVOREL CONTI** patch. However, the usual day of changing patches should be maintained.
It is not necessary to remove the patch during bathing or showering. It is recommended, however, that the patch be removed prior to a sauna bath, and that a new patch is applied immediately thereafter.
If a patch change is missed, the missed patch should be applied as soon as remembered. However, the usual day of changing patches should be maintained. Forgetting a dose may increase the likelihood of break-through bleeding and spotting.

*ELDERLY*:
Data are insufficient in regard to the use of **EVOREL SEQUI** in the elderly (> 65 years old).

**Directions for use/handling**
The **EVOREL SEQUI** should be placed on a clean, dry, healthy, intact area of skin, on the trunk of the body below the waist. Creams, lotions or powders may interfere with the adhesive properties of the patch.
The patch should not be applied on or near the breasts.

The area of application should be changed, with an interval of at least one week allowed between applications to a particular site.
The skin area selected should not be damaged or irritated.
The waistline should not be used because excessive rubbing of the patch may occur.

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

Should a patch fall off, it should be replaced immediately with a new equivalent **EVOREL 50** or **EVOREL CONTI** patch. 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.
When using **EVOREL SEQUI** for the first two weeks, one of the **EVOREL 50** patches should be applied and changed twice weekly.
During the following two weeks of **EVOREL SEQUI**, one of the **EVOREL CONTI** patches should be applied, also to be changed twice weekly. The patient then starts again with a new box **of EVOREL SEQUI**.

To remove the **EVOREL** patch, peel away an edge of the patch and pull smoothly away from the skin. The **EVOREL** patch should be disposed of in household waste (do not flush down the toilet).

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

**SIDE EFFECTS**
Clinical Trial Data
The safety of **EVOREL SEQUI** was evaluated in 165 subjects in 2 active controlled clinical trials. Adverse drug reactions (ADRs) reported for ≥ 1 % of **EVOREL SEQUI**-treated subjects are shown in Table 1.
**Table 1. Adverse Drug Reactions Reported by ≥ 1 % of EVOREL SEQUI-treated Subjects in 2 Clinical Trials of EVOREL SEQUI**

| *System/Organ Class*<br>*Adverse reaction* | *EVOREL SEQUI %*<br>*(N=165)* |
|---|---|
| ***Psychiatric Disorders*** | |
| *Depression* | *5,5* |
| *Insomnia* | *3,6* |
| *Nervousness* | *2,4* |
| *Affect lability* | *1,2* |
| ***Nervous System Disorders*** | |
| *Headache* | *7,9* |
| ***Vascular Disorders*** | |
| *Hypertension* | *4,2* |
| ***Gastrointestinal Disorders*** | |
| *Abdominal pain* | *4,9* |
| *Gastrointestinal Disorder* | *1,8* |
| *Nausea* | *1,8* |
| ***Skin and Subcutaneous Tissue Disorders*** | |
| *Pruritus* | *1,2* |
| *Rash erythematous* | *1,2* |
| ***Musculoskeletal and Connective Tissue Disorders*** | |
| *Arthralgia* | *2,4* |
| ***Reproductive System and Breast Disorders*** | |
| *Breast pain* | *6,1* |
| *Menorrhagia* | *3,0* |
| *Dysmenorrhoea* | *1,2* |
| *Menstrual disorder* | *1,2* |
| ***General Disorders and Administration Site Conditions*** | |
| *Application site reaction* | *14,6* |
| *Oedema* | *2,4* |
| *Malaise* | *1,8* |
| ***Investigations*** | |
| *Increased weight* | *3,0* |

ADRs reported by < 1 % of treated subjects (N = 165) in the above clinical trial dataset are shown in Table 2.

**Table 2. Adverse Drug Reactions Reported by < 1 %treated Subjects in 2 Clinical Trials of EVOREL SEQUI**

| *System/Organ Class* | *Side effect* |
|---|---|
| ***Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)*** | *Breast cancer female, fibroadenoma of breast* |
| ***Psychiatric Disorders*** | *Decreased libido, increased libido.* |
| ***Nervous System Disorders*** | *Disturbance in attention, dizziness* |
| ***Reproductive System and Breast Disorders*** | *Endometrial hyperplasia, metrorrhagia* |
| ***General Disorders and Administration Site Conditions*** | *Fatigue* |

Additional ADRs reported in clinical trials with an oestradiol patch alone in postmenopausal women are shown in Table 3.

**Table 3. Adverse Drug Reactions Reported by EVOREL-treated Subjects in 15 Clinical Trials (N = 2 584) of EVOREL**

| *System/Organ Class* | *Side effect* |
|---|---|
| ***Infections and Infestations*** | *Genital candidiasis* |
| ***Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps*** | *Breast cancer* |
| ***Immune System Disorders*** | *Hypersensitivity* |
| ***Nervous System Disorders*** | *Epilepsy* |
| ***Cardiac Disorders*** | *Palpitations* |
| ***Vascular Disorders*** | *Venous and Arterial Thrombosis and embolism* |
| ***Gastrointestinal Disorders*** | *Diarrhoea, flatulence* |
| ***Skin and Subcutaneous Tissue Disorders*** | *Rash* |
| ***Musculoskeletal and Connective Tissue Disorders*** | *Myalgia* |
| ***General Disorders and Administration Site Conditions*** | *Application site rash*, application site pruritus*, application site erythema*, application site oedema*, generalised oedema, peripheral oedema, pain* |

* Solicited signs/symptoms (recorded as yes/no) in 8 clinical trials of **EVOREL** (N = 1 739).

***Post-marketing Data***
Adverse drug reactions first identified during post-marketing experience with oestradiol are included in Table 4.

**Table 4. Adverse Drug Reactions Identified During Post-Marketing Experience with EVOREL SEQUI Estimated from Spontaneous Reporting Rates**

| | |
|---|---|
| ***Infections and Infestations*** | *Candidiasis* |
| ***Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)*** | *Endometrial cancer* |
| ***Immune System Disorders*** | *Hypersensitivity* |
| ***Psychiatric Disorders*** | *Mood swings*<br>*Severe depression with a higher risk of suicidal thoughts/behavior and suicide* |
| ***Nervous System Disorders*** | *Cerebrovascular accident, migraine, paraesthesia* |
| ***Cardiac Disorders*** | *Palpitations* |
| ***Vascular Disorders*** | *Deep vein thrombosis* |
| ***Respiratory, Thoracic and Mediastinal Disorders*** | *Pulmonary embolism* |
| ***Gastrointestinal Disorders*** | *Abdominal distension* |
| ***Hepatobiliary Disorders*** | *Cholelithiasis* |
| ***Skin and Subcutaneous Tissue Disorders*** | *Stevens-Johnson syndrome* |
| ***Musculoskeletal, Connective Tissue, and Bone Disorders*** | *Back pain* |
| ***Reproductive System and Breast Disorders*** | *Breast enlargement* |
| ***General Disorders and Administration Site Conditions*** | *Application site erythema, application site pruritus, application site rash* |

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS**
Symptoms of overdose of **EVOREL SEQUI** therapy may include nausea, break-through bleeding, breast tenderness, abdominal cramps and/or bloating. These symptoms can be reversed by removing the transdermal patch.

**IDENTIFICATION**
**EVOREL SEQUI** is composed of **EVOREL 50** and **EVOREL CONTI**.

**EVOREL 50** is a flexible, square, colourless adhesive patch of 16 $cm^2$ with convex edges and rounded corners. The adhesive surface of the patch is covered with a protective foil with an S-shaped incision.
Each patch is marked in the centre of the lower margin of the outside of the backing film: CE50.
**EVOREL CONTI** is a flexible, square, colourless adhesive patch of 16 $cm^2$ with convex edges and rounded corners. The adhesive surface of the patch is covered with a protective foil with an S-shaped incision. Each patch is marked in the centre of the lower margin on the outside of the backing film: CEN1.

**PRESENTATION**
One **EVOREL SEQUI** box contains 4 **EVOREL 50** patches and 4 **EVOREL CONTI** patches, packed in individual foil-lined pouches.
The pouch comprises a 4 layer laminate including an aluminium barrier and paper exterior surface.

**STORAGE INSTRUCTIONS**
Store at or below 25 °C. Do not freeze.
**KEEP OUT OF REACH OF CHILDREN**.

**REGISTRATION NUMBER**
31/21.8.2/0538

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION**
Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand 1685
South Africa

**DATE OF PUBLICATION OF THE PACKAGE INSERT**
Date of registration: 16 February 1998
Date of most recently revised Package Insert as approved by council: September 2020

Namibia: NS2 04/21.8.2/0243

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**PATIENT INFORMATION LEAFLET**

**SCHEDULING STATUS**
Schedule 4

**PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM**
**EVOREL® SEQUI** patch

**Read all of this leaflet carefully before you start using EVOREL SEQUI patches**
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **EVOREL SEQUI** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

**1. WHAT EVOREL SEQUI CONTAINS**
Each pack of **EVOREL SEQUI** contains two types of patches:
- **EVOREL 50**
- **EVOREL CONTI**

Each **EVOREL 50** patch contains 3,2 mg of an oestrogen called oestradiol. Each **EVOREL 50** patch delivers 50 micrograms of oestradiol per 24 hours.

Each **EVOREL CONTI** patch contains 3,1 mg oestradiol, formulated as 3,2 mg of oestradiol hemihydrate and 9,82 mg norethisterone, formulated as 11,2 mg norethisterone acetate. Each patch delivers 50 micrograms of oestradiol (an oestrogen) and 170 micrograms of norethisterone (a progestogen hormone) per 24 hours.

**EVOREL 50** and **EVOREL CONTI** patches contain the following inactive ingredients: Acrylate-vinylacetate copolymer (adhesive), guar gum (absorbent) and polyethylene terephthalate foil (backing film).

**2. WHAT EVOREL SEQUI IS USED FOR**
**EVOREL SEQUI** is used for hormone replacement therapy (HRT) in the treatment of symptoms of the menopause such as hot flushes and vaginal dryness in women who still have a womb.
The **EVOREL 50** and the **EVOREL CONTI** patches replace the natural oestrogen that is normally released by the ovaries.
In women who still have a womb, using oestrogen without using a progestogen regularly may cause the lining of the womb to build up and thicken, which may lead to cancer of the womb. It is necessary to shed this lining regularly to prevent any problems occurring. Adding a progestogen hormone to the oestrogen treatment for approximately 2 weeks of a 4-week cycle will cause the lining to be shed to protect the womb.
The shedding of the lining of the womb will produce a withdrawal bleed, so you will probably have a "period" each month starting during week 4, shortly before you finish an **EVOREL SEQUI** pack.

**3. BEFORE YOU APPLY EVOREL SEQUI PATCHES**
**Do not use EVOREL SEQUI if:**
- You are allergic (hypersensitive) to any of the ingredients in **EVOREL 50** and **EVOREL CONTI** patches (see heading "**WHAT EVOREL SEQUI CONTAINS**" above)
- You had, have or suspect that you have breast cancer.
- You have a family history of breast cancer
- You suspect or have oestrogens-dependent malignant tumours (e.g. cancer of womb lining) or pre-malignant tumours (e.g. untreated atypical womb lining overgrowth).
- You have undiagnosed vaginal bleeding.
- You are pregnant or breastfeeding
- You have liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- You had or have venous thromboembolism (deep venous blood clots, blood clots in the lungs)
- You have known conditions that promote blood clotting
- You have active or recent past stroke or heart attack
- You have porphyria
- You have depression, which is not well controlled with treatment
- You have had depression with previous use of oestrogen and/or progesterone/ progestogen containing medicines.

***EVOREL SEQUI and breast cancer:***
Breast cancer has been diagnosed slightly more often in women who use the Pill than in women of the same age who do not use the Pill. This slight increase in the numbers of breast cancer diagnoses gradually disappears during the course of the 10 years after stopping use of the Pill. When you are using **EVOREL SEQUI**, you must perform monthly breast self-examinations. Your doctor will advise you on when to report for breast examinations and any appropriate investigations.

**Before you use EVOREL SEQUI, tell your doctor if:**
- You are known to have inherited genetic changes called "BRCA1 and/or BRCA2 genes
- You started your menstrual periods before the age of 12 years
- You have a history of non-cancerous breast diseases such as atypical hyperplasia or lobular carcinoma in situ
- You had any previous treatment using radiation therapy to the chest or breast
- You have been treated or exposed while in your mother's womb to a medicine called diethylstilboestrol (DES).
- That you are on treatment for depression.
- That you have had depression with previous use of oestrogen and/or progesterone/progestogen containing medicines.
- That you have a substance abuse problem.
- You have underlying psychiatric disorder such as post-traumatic stress disorder or bipolar disorder.
- That you have a family history of mental disorders.
- That you have a history of physical or sexual abuse.

**Depressed mood, depression and the risk of suicidality:**
Oestrogen and/or progesterone/progestogen containing medicines including **EVOREL SEQUI**, may cause mood changes and depression, which may be severe. Severe depression is associated with a higher risk of suicidal thoughts/behavior (e.g. talking about suicide, withdrawing from social contact, having mood swings, being preoccupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. If you experience mood changes and depression contact your doctor for advice.
*Take special care with **EVOREL SEQUI***
- It is important that you have full and thorough physical and gynaecological examination and that your own family's medical histories regarding thrombosis (blood clots) are taken before you start any Hormone Replacement Therapy (HRT).

A careful appraisal of the risk/benefit ratio should be undertaken before the initiation of long-term treatment.
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.

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, you will be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with **EVOREL SEQUI** in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for blood clotting disorders
- Risk factors for oestrogen dependent tumours, e.g. first degree relative with breast cancer
- High blood pressure
- Liver disorders (e.g. benign tumour of the liver)
- Diabetes mellitus
- Gall stones
- Migraine or severe headache
- Systemic lupus erythematosus (Lupus)
- A history of overgrowth of womb lining (endometriosis)
- Epilepsy
- Breast disease

***Conditions which require monitoring by your doctor while on oestrogen therapy:***

- Fluid retention (swelling) from oestrogens, such as in **EVOREL SEQUI**.
- If you have heart or kidney malfunction, it should be carefully monitored.
- Disturbances of liver function.
- History of yellowing of skin and mucous membranes.
- Pre-existing high blood lipids. Rare cases of large increases of blood lipids leading to inflammation of the pancreas have been reported with oestrogen therapy in this condition.

Stop using **EVOREL SEQUI** in case a contraindication is discovered and in the following situations:

- Skin yellowing or deterioration in liver function (jaundice).
- Increase in blood pressure.
- New onset of migraine-type headache.
- Pregnancy occurs.

**Breast cancer**
Long- term use of oestrogen containing HRT products such as in **EVOREL SEQUI** has been associated with an increased risk of ovarian cancer in some epidemiological studies.

You should receive regular full medical examinations whilst using **EVOREL SEQUI**.

- If you have had a blood clot in the leg or lung, a stroke or a heart attack or are bed-ridden for any reason, such as after an operation, you may still be able to use **EVOREL SEQUI** but your doctor should decide on this and you should have a regular medical check up with your doctor if you do use it. If, while using **EVOREL SEQUI**, you develop symptoms of a blood clot such as unexplained pains in the chest, abdomen or legs, the patch should be removed and your doctor contacted immediately.
- The relative risk of heart disease during use of combined oestrogen-progestogen HRT is increased.
- There is an increased risk of stroke in healthy women during treatment with HRT, such as **EVOREL SEQUI**.
- 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.
- There is some evidence of probable dementia in women using continuous combined HRT such as **EVOREL SEQUI**.
- **EVOREL SEQUI** should not be used by children.
- **EVOREL SEQUI** should not be used for contraception.

***Pregnancy and breastfeeding***
Tell your doctor if you are pregnant, or think you are pregnant. You should not use **EVOREL SEQUI** during pregnancy.
You should not breastfeed when using **EVOREL SEQUI**.
Stop using **EVOREL SEQUI** immediately if you fall pregnancy whilst using it.

**Taking other medicines**
Always tell your healthcare professional if you are taking any other medicine (this includes complementary or traditional medicines).
Some medicines can reduce the effect of **EVOREL SEQUI** such as, anti-epilepsy medicines (barbiturates, hydantoins, carbamazepine, meprobamate), phenylbutazone, rifampicin, rifabutin, bosentan, St. John's wort preparations *(Hypericum perforatum)* and certain medicines used for treatment of HIV infections and hepatitis, such as nevirapine and efavirenz.
Ritonavir and nelfinavir may reduce plasma concentrations of the oestrogen component of **EVOREL**, possibly resulting in a decrease in therapeutic effects and unscheduled bleeding. It may also reduce circulating concentrations of the progestin component of **EVOREL SEQUI**, which could result in a diminished protective effect against oestrogen-induced endometrial hyperplasia.

If you are taking any of these medicines, tell your doctor. If you are taking other medicines on a regular basis, including medicines obtained without a prescription, the use of any of these medicines together with **EVOREL SEQUI** can cause undesirable interactions. Please consult your doctor, pharmacist or healthcare professional for advice.

## 4. HOW TO USE EVOREL SEQUI patches

Always use **EVOREL SEQUI** exactly as your doctor has told you. HRT treatment should not be continued for longer than 5 years.

**When to use the patch**
**You MUST use the patches in the correct order as directed by your doctor.**

- For **weeks 1 and 2** you should use the **EVOREL 50** patches
- As soon as you remove your last **EVOREL 50** patch, replace it with one **EVOREL CONTI** patch
- For **weeks 3 and 4** you should use the **EVOREL CONTI** patches.

Start a new pack on **EVOREL SEQUI** as soon as you finish the current one. Do not leave a break between packs.

The instructions below apply to both **EVOREL 50** and **EVOREL CONTI** patches:

- The patches must be changed at 3 or 4-day intervals.
- To make it easy to remember when this should be done, keep to the same two days every week. This will mean that one patch is on for three and the other for four days. For example, if you use your first patch on a Monday, it should be changed on Thursday and again on the following Monday.
- You can work out the two days of your own schedule from the following table, starting from the first day of use:

| If you put your first patch on: | Change on | Change again on |
|---|---|---|
| Monday | Thursday | Monday |
| Tuesday | Friday | Tuesday |
| Wednesday | Saturday | Wednesday |
| Thursday | Sunday | Thursday |
| Friday | Monday | Friday |
| Saturday | Tuesday | Saturday |
| Sunday | Wednesday | Sunday |

**To help you to remember your "two patch change" days, mark them as shown:**

| Mon | Tues | Wed | Thur | Fri | Sat | Sun |
|---|---|---|---|---|---|---|
| Thur | Fri | Sat | Sun | Mon | Tue | Wed |

**How to put the EVOREL 50 and EVOREL CONTI patches on**
The patch should be applied to clean, dry skin but not on top of cuts, spots or other skin blemishes or on an area where you have just applied cream, moisturiser or talc. The patch should be applied to the skin as soon as it is removed from the wrapper and applied as described below:

(a) Tear open the wrapper, first between the "V's" along one edge and then along the other edge. Take out the patch.
(b) With the backing foil facing you, bend the patch and peel off one half of the foil. **Do not touch the sticky side of the patch** otherwise it may not stick properly.
(c) Apply the open half of the patch to your skin, remove the other half of the foil and press down the rest of the patch.
(d) Press the patch with the palm of your hand to ensure it is firmly stuck to the skin.
(e) To remove, peel away an edge of the patch and pull smoothly away from the skin.
(f) You may use soap and water to help remove any gum/glue, which may remain on your skin after patch removal.

**Where to place the patch**
Stick the patch onto hairless area of skin below the waist. Most women prefer to wear the patch on the thigh or bottom. **It should never be worn on or near the breasts.** Although it can be worn underneath clothing, it should not be placed under elasticated waistbands.
The patch should not be placed on the same area of skin twice in a row.

**What if the patch falls off?**
Just apply a new patch of the **same type**, preferably taken from a spare pack. If this is not possible or leaves you without adequate supplies, contact your doctor.

**What if I forget to change the patch?**
Just change it as soon as possible and then keep to your original "patch change" days.
Forgetting a dose may increase the likelihood of break-through bleeding and spotting.

**Can I wash, bath or shower as normal?**
YES, but do not scrub too hard in case you loosen the edges of the patch.

**Can I go swimming with the patch on?**
YES, the patch will not be affected.

**Can I exercise or play sports?**
YES, but try to avoid wearing it under tight clothing or waistband.

**Can I sunbathe with the patch on?**
YES, but keep the patch covered to avoid direct sunlight.

**What if I am allergic to the patch?**
Allergic reactions to the patch may occur. Should you have such a reaction, please consult your doctor.

**Does the patch work as a contraceptive?**
NO, the levels of hormone supplied by the **EVOREL SEQUI** patch are too low for it to do this. Although menopausal women face an ever-decreasing risk of pregnancy, normal precautions should be taken during sexual intercourse. If in doubt, talk to your doctor.

**What do you do in the case of an overdose?**
Overdose with the patch is unlikely. Effects of too much **EVOREL SEQUI** can be reversed simply by removal of the patch. The most common symptoms of **EVOREL SEQUI** overdose are breast tenderness, nausea, irregular bleeding, stomach pain and /or bloating.

## 5. POSSIBLE SIDE EFFECTS

**EVOREL SEQUI** can cause some unwanted effects.
The unwanted effects include the following:
Data from clinical trials:
***Frequent:***

- Depression
- Sleeplessness
- Nervousness
- Emotional incontinence (involuntary emotions)
- Headache
- High blood pressure
- Abdominal pain
- Digestive tract Disorder
- Feeling sick
- Itching
- Red skin rash
- Joint pain
- Breast pain
- Abnormal menstrual period (heavy and or prolonged)
- Painful menstruation
- Menstrual disorder (Irregular, heavy or prolonged bleeding from the vagina)
- Application site reaction – this includes sensitivity, redness, swelling and/or itchiness on the skin where the patch was placed
- Swelling may occur on the skin where the patch was placed
- Generalised feeling of discomfort
- Increased weight

***Less frequent:***

- Female breast cancer, noncancerous (benign) tumour of breast
- Low sex drive, increased sex drive.
- Disturbance in attention, dizziness
- Excessive growth of womb lining, breakthrough bleeding or spotting
- Fatigue
- Suicidal thoughts/behaviour and suicide

***Unwanted Effects Reported by EVOREL-treated Subjects in 15 Clinical Trials of EVOREL:***

- Genital/vaginal fungal thrush infection
- Breast cancer
- Allergic reactions - sudden swelling of the face or throat which may cause difficulty in swallowing or breathing. This may be a sign of an allergic reaction
- Epilepsy
- Abnormal heart beat
- Blood clots in deep veins
- Frequent and loose watery stools with excessive gas in stomach or intestines
- Rash
- Muscle pain
- Generalised swelling
- Tissue oedema
- Pain

** Solicited signs/symptoms (recorded as yes/no) in 8 clinical trials of **EVOREL**.*

- Vaginal thrush
- Womb cancer
- Allergic reactions - sudden swelling of the face or throat which may cause difficulty in swallowing or breathing. This may be a sign of an allergic reaction
- Mood swings
- Stroke, migraine, burning or prickling sensation
- Abnormal heart beat
- Blood clots in deep veins of lower legs
- Blood clots in the lungs
- Abdominal distension
- Gall stones
- Stevens- Johnson syndrome (Extremely serious allergic reaction involving skin and mucous membranes)
- Back pain
- Breast enlargement
- Application site redness, application site itching, application site rash

If you develop skin rashes or irritation, where you applied the patch, remove the patch and ask your doctor for advice. If you notice any other symptoms not listed above whilst using the patch, please tell your doctor about them.
Not all side effects reported for **EVOREL SEQUI** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice

## 6. STORING AND DISPOSING OF EVOREL SEQUI

**EVOREL SEQUI** should be stored at room temperature (i.e. at or below 25 °C). Do not freeze. Keep used and unused patches out of reach of children and pets – put used patches in the bin you use for household rubbish. Do not flush down the toilet.

**Other important information:**
Do not use the patches:
⌦ After the expiry date shown on the label
⌦ If the protective sachet/pouch is open

## 7. PRESENTATION OF EVOREL SEQUI

**EVOREL SEQUI** comes in a memory pack containing four **EVOREL 50** patches and four **EVOREL CONTI** patches. Each patch comes in a protective sealed pouch.

## 8. IDENTIFICATION OF EVOREL SEQUI

**EVOREL 50** and **EVOREL CONTI** patches are square shaped, transparent patches with a self-adhesive backing, which can be stuck to the skin.

**EVOREL 50** is marked CE50 and has a surface area of 16 $cm^2$.
**EVOREL CONTI** is marked CEN1 and has a surface area of 16 $cm^2$.

In each patch the active ingredients are spread evenly in the adhesive and pass slowly through the skin into the body.

## 9. REGISTRATION NUMBER

**EVOREL SEQUI**: 31/21.8.2/0538

## 10. NAME AND BUSINESS ADDRESS OF THE REGISTRATION HOLDER

Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand 1685
South Africa
011 635 0000

## 11. DATE OF PUBLICATION

Date of registration: 16 February 1998
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Namibia: NS2 04/21.8.2/0243

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**PASIËNTINLIGTINGSBLAD**

**SKEDULERINGSTATUS**
Skedule 4

**HANDELSNAAM, STERKTE EN DOSERINGSVORM**
**EVOREL® SEQUI** plakker

**Lees die hele pamflet deeglik deur voordat jy begin om EVOREL SEQUI plakkers te gebruik.**

- Hou hierdie pamflet. Dit is moontlik dat jy dit weer sal wil deurlees.
- Indien jy nog vrae het, raadpleeg asseblief jou dokter of apteker.
- **EVOREL SEQUI** is vir jou persoonlik voorgeskryf en jy moet nie jou medisyne met ander mense deel nie. Dit kan skadelik vir hulle wees, selfs al is hulle simptome dieselfde as joune.

## 1. WAT EVOREL SEQUI BEVAT

Elke pakkie met **EVOREL SEQUI** bevat twee soorte plakkers:

- **EVOREL 50**
- **EVOREL CONTI**

Elke **EVOREL 50** plakker bevat 3,2 mg van 'n estrogeen, genaamd estradiol. Elke **EVOREL 50** plakker lewer 50 mikrogram estradiol per 24 uur.

Elke **EVOREL CONTI** plakker bevat 3,1 mg estradiol geformuleer as 3,2 mg estradiolhemihidraat en 9,82 mg noretisteroon, geformuleer as 11,2 mg noretis-teroonasetaat. Elke plakker lewer 50 mikrogram estradiol ('n estrogeen) en 170 mikrogram noretisteroon ('n progestogeenhormoon) per 24 uur.

**EVOREL 50** en **EVOREL CONTI** plakkers bevat die volgende onaktiewe bestanddele: akrilaat-vinielasetaat-kopolimeer (kleefmiddel), guargom (absorbeerder) en poliëtileen tereftalaatfoelie (steunlaag).

## 2. WAARVOOR EVOREL SEQUI GEBRUIK WORD

**EVOREL SEQUI** word gebruik vir hormoonvervangingsterapie (HVT) by die behandeling van die simptome van die menopouse, soos warmgloede en vagi- nale droogheid by vrouens wat nog 'n baarmoeder het.

Die **EVOREL 50** en **EVOREL CONTI** plakkers vervang die natuurlike estrogeen wat normaalweg deur die eierstokke vrygestel word.

By vroue wat nog 'n baarmoeder het, kan die gebruik van 'n estrogeen sonder om 'n progestageen te gebruik, veroorsaak dat die voering in die baarmoeder kan opbou en verdik, wat dan kan lei tot baarmoederkanker. Dit is nodig dat hierdie voering gereeld afgewerp word om moontlike probleme te voorkom. Die toevoeging van 'n progestageenhormoon tot die estrogeenbehandeling vir ongeveer 2 weke van 'n 4-week siklus sal meebring dat die voering afgewerp word om die baarmoeder te beskerm.

Die afwerping van die voering van die baarmoeder sal onttrekkingsbloeding veroorsaak, dus sal jy waarskynlik elke maand jou maandstonde gedurende week-4 hê, net voordat jy klaar is met 'n **EVOREL SEQUI** pakkie.

## 3. VOORDAT JY EVOREL SEQUI PLAKKERS OPPLAK

**Moenie EVOREL SEQUI gebruik nie, indien:**

- Jy allergies (hipersensitief) is vir enige van die bestanddele in **EVOREL 50** en **EVOREL CONTI** plakkers nie (kyk hierbo, by die opskrif "**WAT EVOREL SEQUI BEVAT**").
- Jy borskanker het, of vermoed dat jy dit het.
- Jy het 'n familiegeskiedenis van borskanker.
- Jy estrogeen-afhanklike kwaadaardige gewasse (bv. kanker van die baar-moedervoering) het, of vermoedelik het, of gewasse wat kanker kan vooraf-gaan (bv. onbehandelde atipiese oorgroeiing van die baarmoedervoering).
- Jy ongediagnoseerde vaginale bloeding het.
- Jy swanger is of borsvoed.
- Jy lewersiekte, of 'n geskiedenis van lewersiekte het, solank die lewerfunk-siewaardes nie genormaliseer het nie
- Jy veneuse tromboëmbolisme (bloedklonte in die diepliggende are, bloed-klonte in die longe) het, of gehad het.
- Jy bekende siektetoestande het wat bloedstolling bevorder
- Jy tans beroerte of 'n hartaanval het, of onlangs gehad het
- Jy porfirie het.
- Jy depressie het, wat nie goed beheer word met behandeling nie.
- Jy het depressie met vorige gebruik van estrogeen- en/ of progesteroon/ progestogeenbevattende medisyne gehad.

**EVOREL SEQUI en borskanker:**

Borskanker is meer gereeld gediagnoseer in vrouens wat die Pil gebruik as by vrouens van dieselfde ouderdom wat nie die Pil gebruik nie. Hierdie effense toename in die aantal borskankerdiagnoses verdwyn geleidelik gedurende die 10 jaar nadat die gebruik van die Pil gestop is. Wanneer jy **EVOREL SEQUI** gebruik, moet jy bors selfondersoeke maandelikse genaamd doen. Jou dokter sal u adviseer oor wanneer jy vir borsondersoeke en enige toepaslike ondersoeke moet aanmeld.

**Voordat jy EVOREL SEQUI gebruik, vertel jou dokter indien:**

- Dit bekend is dat jy genetiese veranderinge geërf het, "BRCA1 en/of BRCA2 gene".
- Jy jou menstruele periodes voor die ouderdom van 12 jaar begin het.
- Jy 'n geskiedenis van nie-kankeragtige borssiektes soos atipiese hiperplasie of lobulêre karsinoom in situ het nie.
- Jy enige vorige behandeling, wat bestralingterapie van die bors gebruik, gehad het.
- Jy behandel of blootgestel aan medisyne genaamd dietielstilboestrol (DES) was terwyl jy in jou moeder se baarmoeder was.
- Jy op behandeling vir depressie is.
- Jy depressie gehad het met vorige gebruik van estrogeen- en/of progesteroon/ progestageenbevattende medisyne.
- Jy 'n dwelmmisbruikprobleem het.
- Jy onderliggende psigiatriese versteuring soos posttraumatiese sresversteuring of bipolêre versteuring het.
- Jy 'n familiegeskiedenis van geestesversteurings het.
- Jy 'n geskiedenis vanf fisiese of seksuele mishandeling het.

**Depressiewe bui, depressie en die risiko van selfmoord:**
Estrogeen- en/of progesteroon/progestageenbevattende medisyne, insluitend **EVOREL SEQUI**, kan bui-veranderinge en depressie veroorsaak, wat ernstig kan wees. Erge depressie hou verband met 'n hoër risiko van selfmoordgedagtes/gedrag (bv. praat oor selfmoord, ontrekking van sosiale kontak, buierigheid, behep met die dood of geweld, hopeloos voel oor 'n situasie, toenemende gebruik van alkohol/ dwelms, doen selfvernietigende dinge, persoonlikheidsveranderings) en selfmoord. Indien jy buierigheid of depressie ervaar, kontak jou dokter vir advies.

*Neem spesiale voorsorg met EVOREL SEQUI*

- Dit is belangrik dat jy 'n volledige en deeglike fisiese en ginekologiese onder-soek ondergaan en dat die mediese geskiedenis van jou eie familie betref-fende trombose (bloedklonte) in ag geneem word voordat jy met enige hor-moonvervangingsterapie (HVT) begin.

'n Deeglike bepaling van die risiko/voordeelverhouding moet voor aanvang van langtermynbehandeling gedoen word.

Inligting oor risiko's wat verband hou met HVT by die behandeling van ver- vroegde menopouse, is beperk. Vanweë die lae absolute risiko by jonger vrouens kan die balans van die voordele en risiko's vir hierdie vrouens egter meer gunstig wees as by ouer vrouens.

Indien enige van die volgende siektetoestande teenwoordig is, voorheen gebeur het en/of vererger het tydens swangerskap of vorige hormoonbehande- ling, sal jy deeglike toesig ontvang. Dit moet in ag geneem word dat hierdie toe- stande weer kan voorkom, of kan vererger tydens behandeling met **EVOREL SEQUI**, in besonder:

- Leiomioom (baarmoederveselspiergewasse) of endometriose
- Risikofaktore vir bloedstollingsiektes
- Risikofaktore vir estrogeengevoelige gewasse, bv. eerstegraadse familielid met borskanker
- Hoë bloeddruk
- Lewersiektes (bv. 'n goedaardige gewas van die lewer)
- Diabetes mellitus
- Galstene
- Migraine, of ernstige hoofpyn
- Sistemiese lupus eritematose (lupus).
- 'n Geskiedenis van oorgroeiing van die baarmoedervoering (endometriose)
- Epilepsie
- Borssiekte

*Siektetoestande wat monitering deur jou dokter tydens estrogeenbe- handeling benodig:*

- Vloeistofretensie (swelling) vanweë estrogene, soos **in EVOREL SEQUI**.
- Indien jou hart of niere nie goed werk nie, moet dit deeglik gekontroleer word.
- Versteurings van die lewerfunksie.
- 'n Geskiedenis van geel verkleuring van die vel en slymvliese.
- Voorafbestaande hoë bloedvette. Seldsame gevalle van aansienlike toena-mes in bloedvette, wat tot ontsteking van die pankreas lei, is by hierdie siek-tetoestand met estrogeenbehandeling aangemeld.

Staak die gebruik van **EVOREL SEQUI** ingeval daar 'n teenaanwysing ontdek word, en onder die volgende omstandighede:

- Vergeelde vel of agteruitgang van die lewerfunksie (geelsug).
- Toename in bloeddruk.
- Nuwe aanvang van migraine-tipe hoofpyn.
- Swangerskap plaasvind.

**Borskanker**
Langdurige gebruik van estrogeen-bevattende HVT produkte, soos **EVOREL SEQUI**, is in sommige epidemiologiese navorsingstudies in verband gebring met 'n verhoogde risiko vir ovariumkanker.
Jy moet gereeld volledige mediese ondersoeke ondergaan terwyl jy **EVOREL SEQUI** gebruik.

- As jy 'n bloedklont in die been of long gehad het, of 'n beroerte of 'n hartaan-val kry, of om die een of ander rede bedlêend is, soos ná 'n operasie, mag dit steeds moontlik wees dat jy **EVOREL SEQUI** kan gebruik, maar jou dok- ter moet hieroor besluit en jy moet dan gereelde mediese ondersoeke by jou dokter ondergaan. As jy, terwyl jy **EVOREL SEQUI** gebruik, simptome van 'n bloedklont ontwikkel, soos onverklaarbare pyne in die bors, buik of bene, moet die plakker verwyder word en jou dokter dadelik gekontak word.
- Die relatiewe risiko van hartsiekte tydens die gebruik van gekombineerde estrogeen-progestageen HVT is hoër.
- Daar is 'n verhoogde risiko vir beroerte by gesonde vroue tydens behande- ling met HVT, soos **EVOREL SEQUI**.
- Gekombineerde estrogeen-progestageenbehandeling en estrogeen mono-terapie is geassosieer met 'n tot 1,5-voudige hoër risiko vir 'n iskemiese beroerte. Die relatiewe risiko verander nie met die ouderdom of met die tyd na die menopouse nie. Omdat die absolute risiko op 'n beroerte by basislyn egter sterk ouderdomsverwant is, sal die algehele risiko op 'n beroerte by vroue wat HVT gebruik, toeneem met ouderdom.
- Daar is 'n mate van bewys van waarskynlike demensie by vroue wat onafge-broke gebruik maak van gekombineerde HVT, soos **EVOREL SEQUI.**
- **EVOREL SEQUI** moet nie deur kinders gebruik word nie.
- **EVOREL SEQUI** moet nie vir voorbehoeding gebruik word nie.

***Swangerskap en borsvoeding***
Lig jou dokter in as jy swanger is, of dink jy is swanger. Jy moet **nie EVOREL SEQUI** gebruik nie.
Jy moet nie borsvoed terwyl jy **EVOREL SEQUI** gebruik nie.
Staak dadelik die gebruik van **EVOREL SEQUI** as jy swanger raak terwyl jy dit gebruik.

**Die gebruik van ander medisynes**
Lig altyd jou gesondheidsorgkundige in as jy enige ander medisyne neem. (Dit sluit in komplementêre of tradisionele medisynes)
Sommige medisynes kan die effek van **EVOREL SEQUI** verminder, soos anti-epileptiese medisynes (barbiturate, hidantoïene, karbamasepien, megro- bamaat), fenielbutasoon, rifampisien, rifabutien, bosentaan, produkte met Sint-johanneskruid (Hypericum perforatum) en sekere medisynes vir die behandeling van MIV-infeksies, soos nevirapien en efavirens.

Ritonavir en nelfinavir kan die plasmakonsentrasies van die estrogeenkompo-nent van **EVOREL** verminder, wat moontlik kan lei tot verminderde terapeutiese effek en onbeplande bloeding. Dit kan ook sirkulerende konsentrasies van die progestienkomponent van **EVOREL SEQUI** verminder, wat kan lei tot 'n vermin-derde beskermende effek teen die endometriale hiperplasie wat deur estro- geen veroorsaak word.

As jy enige van hierdie medisynes neem, lig jou dokter in. As jy gereeld ander medisyne gebruik, insluitende medisyne wat sonder voorskrif verkry is, kan die gebruik van enige van hierdie medisynes saam met **EVOREL SEQUI** onge-wenste interaksies veroorsaak. Raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgkundige.

## 4. HOE OM EVOREL SEQUI PLAKKERS TE GEBRUIK

Gebruik **EVOREL SEQUI** altyd presies soos jou dokter vir jou gesê het. HVT moet nie vir langer as 5 jaar gebruik word nie.
**Wanneer om die plakker te gebruik**
**Jy MOET die plakkers in die korrekte volgorde, soos jou dokter voorgeskryf het, gebruik.**

- Vir **week 1 en 2** moet jy die **EVOREL 50** plakkers gebruik
- Sodra jy die laaste **EVOREL 50** plakker afgehaal het, vervang dit met een **EVOREL CONTI** plakker
- Vir **week 3 en 4** moet jy die **EVOREL CONTI** plakkers gebruik.

Begin met 'n nuwe pakkie **EVOREL SEQUI** sodra jy die huidige een opgebruik het. Moenie toelaat dat daar tyd verloop tussen pakkies nie.
Die aanwysings hieronder is op beide **EVOREL 50** en **EVOREL CONTI** plakkers van toepassing:

- Die plakkers moet met 3- of 4-dag tussenposes vervang word.
- Om dit makliker te maak om te onthou wanneer dit gedoen moet word, bly by dieselfde twee dae elke week. Dit sal beteken dat een plakker vir drie dae, en die ander een vir vier dae op is. Byvoorbeeld, as jy jou eerste plak- ker op 'n Maandag opgeplak het, moet dit op Donderdag vervang word en dan weer op die volgende Maandag.
- Jy kan jou eie twee dae self volgens die volgende tabel skeduleer; begin vanaf die eerste dag van gebruik:

| Indien jy jou eerste plakker opplak op: | Verander op | Verander weer op |
|---|---|---|
| Maandag | Donderdag | Maandag |
| Dinsdag | Vrydag | Dinsdag |
| Woensdag | Saterdag | Woensdag |
| Donderdag | Sondag | Donderdag |
| Vrydag | Maandag | Vrydag |
| Saterdag | Dinsdag | Saterdag |
| Sondag | Woensdag | Sondag |

**Om jou te help om jou "twee plakker-vervangingsdae" te onthou, merk hulle soos volg:**

| Mo | Di | Wo | Do | Vr | Sa | So |
|---|---|---|---|---|---|---|
| Do | Vr | Sa | So | Ma | Di | Wo |

**Hoe om die EVOREL 50 en EVOREL CONTI plakkers op te plak**
Die plakker moet op 'n skoon, droë vel geplak word, maar nie op snye, vlekke of ander velletsels nie, of op 'n gebied waar jy pas room, bevogtiger of talk aan- gewend het nie.
Die plakker moet, sodra dit uit die verpakking verwyder is, soos volg op die vel geplak word:

(a) Skeur die omhulsel oop, eers tussen die "V's" aan die een kant en dan langs die ander kant. Haal die plakker uit.
(b) Met die rugkant se foelie na jou kant toe, buig die plakker en trek die een helfte van die foelie af. **Moenie raak aan die klewerige kant van die plakker** nie, anders sal dit dalk nie goed plak nie.
(c) Plak die oop helfte van die plakker op jou vel, verwyder dan die ander helfte van die foelie en druk die res van die plakker vas.
(d) Druk op die plakker met die handpalm, om seker te maak dit sit stewig vas aan die vel.
(e) Om te verwyder, wikkel die rand van die plakker los en trek dit dan egalig van die vel af.
(f) Jy kan seep en water gebruik om te help om enige gom/lym wat op jou vel agterbly nadat die plakker af is, te verwyder.

**Waar om die plakker te plaas**
Plak die plakker op 'n haarlose gebied van die vel, onder die middellyf. Meeste vrouens verkies om die plakker op die dy of boud te dra. **Dit moet nooit op, of naby die borste geplak word nie**. Hoewel dit onder klere gedra kan word, moet dit nie onder rekkerige gordels geplak word nie.
Die plakker moet nie twee opeenvolgende kere op dieselfde plek op die vel geplak word nie.

**Wat om te doen as die plakker afval?**
Plak net 'n nuwe plakker van dieselfde soort op, verkieslik uit 'n spaarpakkie geneem. As dit nie moontlik is nie, of jou sonder voldoende voorraad laat, kon- tak jou dokter.

**Wat gebeur as ek vergeet om die plakker te vervang?**
Verander dit sodra moontlik en hou dan by jou oorspronklike "plakker-vervangingsdae".
As 'n dosis vergeet word, kan dit die moontlikheid van deurbraakbloeding en spikkelbloeding verhoog.

**Kan ek was, bad en stort soos gewoonlik?**
JA, maar moenie te hard vryf nie, vir ingeval jy die rante van jou plakker laat loskom.

**Kan ek swem met die plakker op?**
JA, die plakker sal nie aangetas word nie.

**Kan ek oefen of sport beoefen?**
JA, maar probeer vermy om dit onder stywe klere of gordels te dra.

**Kan ek sonbaai met die plakker op?**
JA, maar hou die plakker toe om dit teen direkte sonlig te beskerm.

**Wat gebeur as ek allergies is vir die plakker?**
Allergiese reaksies vir die plakker kan voorkom. Indien jy so 'n reaksie het, raadpleeg asseblief jou dokter.

**Werk die plakker as 'n voorbehoedmiddel?**
NEE, die hormoonvlakke wat deur die **EVOREL SEQUI** plakker verskaf word is te laag daarvoor. Alhoewel menopousale vroue 'n steeds-afnemende risiko loop vir swangerskap, moet normale voorsorg tydens seksuele omgang getref word. Indien jy twyfel, raadpleeg jou dokter

**Wat doen jy in geval van 'n oordosering?**
Oordosering met die plakker is onwaarskynlik. Die uitwerking van te veel **EVOREL SEQUI** kan omgekeer word deur eenvoudig die plakker te verwyder. Die mees algemene simptome van oordosering met **EVOREL SEQUI** is gevoe- lige borste, naarheid, ongereelde bloeding, maagpyn en/of buikopsetting.

## 5. MOONTLIKE NEWE-EFFEKTE

**EVOREL SEQUI** kan sekere ongewenste effekte hê. Die ongewenste effekte sluit die volgende in:
Data uit kliniese studies:
**Dikwels:**

- Depressie
- Slapeloosheid
- Senuweeagtigheid
- Emosionele onbeheerstheid (onwillekeurige emosies)
- Hoofpyn
- Hoë bloeddruk
- Buikpyn
- Omgekrapte spysverteringskanaal
- Mislike gevoel
- Jeuk
- Rooi veluitslag
- Gewrigspyn
- Borspyn
- Abnormale maandstondes (swaar en/of langdurig)
- Pynlike menstruasie
- Menstruele afwyking (ongereelde, swaar of langdurige bloeding uit die vagina)
- Reaksie by die plek van aanwending - dit sluit in gevoeligheid, rooiheid, swelling en/of jeukerigheid van die vel waar die plakker geplak was
- Swelling kan op die vel voorkom waar die plakker geplaas was
- Algemene gevoel van ongemak
- Toename in gewig

**Minder dikwels:**

- Borskanker by vrouens, nie-kankeragtige (goedaardige) gewas van die bors
- Lae seksdrang, verhoogde seksdrang
- Aandaggebrek, duiseligheid
- Buitensporige groei van die baarmoedervoering, deurbraakbloeding of spik-kelbloeding
- Moegheid
- Selfmoord gedagtes/gedrag en selfmoord

**Ongewenste uitwerkings aangemeld deur proefpersone wat met EVOREL behandel is in 15 kliniese proewe met EVOREL:**

- Genitale/vaginale swam/sproei infeksie
- Borskanker
- Allergiese reaksies - skielike swelling van die gesig of keel, wat probleme om te sluk of asem te haal kan veroorsaak. Dit kan 'n teken wees van 'n aller- giese reaksie
- Epilepsie
- Abnormale hartslag
- Bloedklonte in die diepliggende are
- Gereelde en los waterige stoelgange met buitensporige gas in die maag of derms
- Veluitslag
- Spierpyn
- Algemene swelling
- Weefsel edeem
- Pyn

** Aangevraagde tekens/simptome (aangeteken as ja/nee) in 8 kliniese proewe met **EVOREL**.*

- Vaginale sproei
- Baarmoederkanker
- Allergiese reaksies - skielike swelling van die gesig of keel, wat probleme om tydens swangerskap gebruik nie.
- Gemoedskommelings
- Beroerte, migraine, brandende of stekerige gevoel
- Abnormale hartslag
- Bloedklonte in diepliggende are van die onderbene
- Bloedklonte in die longe
- Opgehewe buik
- Galstene
- Stevens-Johnson-sindroom (uiters ernstige allergiese reaksie wat die vel en slymvliese betrek)
- Rugpyn
- Vergrote borste
- Rooiheid by die plek van toediening, jeukerigheid by die plek van toediening, uitslag by plek van toediening

As jy veluitslag of irritasie ontwikkel waar jy die plakker opgesit het, verwyder die plakker en kry raad by jou dokter. Indien jy terwyl jy die plakker gebruik enige ander simptome waarneem wat nie hierbo gelys is nie, sê asseblief vir jou dokter daarvan.
Nie alle newe-effekte wat vir **EVOREL SEQUI** aangemeld is, is by hierdie inlig-tingsblad ingesluit nie. Indien jou algemene gesondheid agteruitgaan of jy enige ongunstige effekte ervaar terwyl jy hierdie medisyne ontvang, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgkundige

## 6. BERGING EN WEGDOENING VAN EVOREL SEQUI

**EVOREL SEQUI** moet by kamertemperatuur (d.i. by, of benede 25 °C) bewaar word. Moenie vries nie. Bewaar gebruikte en ongebruikte plakkers buite die bereik van kinders en troeteldiere - gooi gebruikte plakkers in die huishoudelike vullisblik. Moenie dit in die toilet wegspoel nie.
**Ander belangrike inligting:**
Moenie die plakkers gebruik nie:
⌦ Na die vervaldatum wat op die etiket verskyn
⌦ Indien die beskermende sakkie/omhulsel oop is

## 7. AANBIEDING VAN EVOREL SEQUI

**EVOREL SEQUI** word verskaf in 'n onthou-pakkie met vier **EVOREL 50** plakkers en vier **EVOREL CONTI** plakkers. Elke plakker word verskaf in 'n besker- mende verseëlde sakkie.

## 8. IDENTIFIKASIE VAN EVOREL SEQUI

**EVOREL 50** en **EVOREL CONTI** plakkers is vierkantige, deursigtige plakkers met 'n selfklewende kant, wat op die vel geplak kan word.
**EVOREL 50** is gemerk met CE50 en het 'n oppervlakte van 16 $cm^2$.
**EVOREL CONTI** is gemerk met CEN1 en het 'n oppervlakte van 16 $cm^2$.

In elke plakker is die aktiewe bestanddele eweredig in die kleeflaag versprei, waarvandaan dit stadig deur die vel geabsorbeer word om in die liggaam te kom.

## 9. REGISTRASIENOMMER

**EVOREL SEQUI**: 31/21.8.2/0538

## 10. NAAM EN BESIGHEIDSADRES VAN DIE REGISTRASIEHOUER:

Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand
1685
South Africa
www.adcock.com

## 11. DATUM VAN PUBLIKASIE

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Datum van mees onlangs hersiene pasiëntinligtingsblad soos goedgekeur deur die Raad: September 2020

Namibië: NS2 04/21.8.2/0243

adcock ingram