SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

EVOREL® 25, 25 µg patches

EVOREL® 50, 50 µg patches

EVOREL® 75, 75 µg patches

EVOREL® 100, 100 µg patches

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EVOREL 25 (8 cm^2) patch contains 1,55 mg of estradiol, formulated as 1,6 mg of estradiol hemihydrate. Each EVOREL 25 patch delivers 25 µg of estradiol per 24 hours.

EVOREL 50 (16 cm^2) patch contains 3,10 mg estradiol, formulated as 3,2 mg of estradiol hemihydrate. Each EVOREL 50 patch delivers 50 µg of estradiol per 24 hours.

EVOREL 75 (24 cm^2) patch contains 4,65 mg estradiol, formulated as 4,8 mg of estradiol hemihydrate. Each EVOREL 75 patch delivers 75 µg of estradiol per 24 hours.

EVOREL 100 (32 cm^2) patch contains 6,20 mg estradiol, formulated as 6,4 mg of estradiol hemihydrate. Each EVOREL 100 patch delivers 100 µg of estradiol per 24 hours.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Matrix type transdermal patches.

EVOREL 25 is an adhesive square patch of 8 cm^2 with rounded corners. The outside of the backing film is marked CE25 on the distal side.

EVOREL 50 is an adhesive square patch of 16 cm^2 with rounded corners. The outside of the backing film is marked CE50 on the distal side.

EVOREL 75 is an adhesive square patch of 24 cm^2 with rounded corners. The outside of the backing film is marked CE75 on the distal side.

EVOREL 100 is an adhesive square patch of 32 cm^2 with rounded corners. The outside of the backing film is marked CE100 on the distal side.

The adhesive surface of the patch is covered with a protective foil with an S-shaped incision with dimples around the edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of symptoms associated with menopause, either due to menopausal cessation of estrogen production and secretion, or surgical removal of the ovaries.

In women with an intact uterus, a progestogen must be used as adjunct therapy for the prevention of endometrial hyperplasia and cancer.

Prevention of estrogen dependent post-menopausal osteoporosis.

Treatment should not be continued for more than 5 years.

4.2 Posology and method of administration

Posology

Adults

In patients using oral estrogens, treatment with EVOREL can be initiated one week after withdrawal.

EVOREL should be applied twice weekly, i.e. the patch should be changed every 3 to 4 days. EVOREL is administered in a cyclic manner, 3 weeks of treatment (6 applications) followed by an interval of one week without treatment. During this treatment-free week vaginal withdrawal bleeding *may* occur.

Continuous non-cyclic therapy may be indicated in hysterectomised women and if climacteric symptoms occur during the treatment-free week.

Treatment is usually initiated with EVOREL 50. In further treatment courses, the dosage should be individually adapted. For treatment of post-menopausal symptoms the lowest effective dose should be used.

EVOREL should not be continued for longer than 5 years.

EVOREL 25 should be administered only to those patients who cannot tolerate the higher dose.

Breast discomfort, breakthrough bleeding, water retention or bloating (if persisting for more than 6 weeks) are generally signs that the dose is too high and needs to be lowered. If, after 2 to 3 weeks, the dose selected fails to eliminate the signs and symptoms of estrogen deficiency, a higher dose should be given.

For maintenance, one should always use the lowest effective dose therapy. For prevention of bone loss, EVOREL 50, 75 or 100 are recommended. The dose of 100 µg of estradiol/24 hours should not be exceeded. Note that for women with a uterus, EVOREL 75 and EVOREL 100 are not recommended, as the endometrial safety of added progestogen has not been studied for transdermal doses of estradiol above 50 µg/day.

Progestogen treatment is recommended in any woman with a uterus:

- during 12 to 14 consecutive days of the calendar month during uninterrupted EVOREL treatment.
- or during the last 12 to 14 days (i.e. starting on cycle days 8 or 10) of the 21-day cycle during which treatment with EVOREL is provided.

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

Vaginal bleeding will normally occur after the start of the progestogen treatment.

Special populations

Liver or kidney function impairment

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

Elderly

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

Method of administration

Transdermal use.

Administration instructions

The EVOREL patch 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 of 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 the 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 be avoided and the palm of the hand used to press the patch onto the skin and to bring the patch to skin temperature at which the adhesive effect is optimised.

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

Should a patch fall off, a new patch should be applied immediately. However, the usual day of changing patches should be maintained. It is not necessary to remove the patch during bathing and showering. It is recommended, however, that the patch be removed prior to sauna bath, and the 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 breakthrough bleeding and spotting.

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

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.

4.3 Contraindications

- Known hypersensitivity to estrogen or to any of the inactive ingredients of EVOREL listed in section 6.1.
- Known current or past or suspected breast cancer.
- Family history of breast cancer.

- Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer) or pre-malignant tumours (e.g. untreated atypical endometrial hyperplasia).
- Undiagnosed genital bleeding.
- EVOREL must not be used during pregnancy or lactation (see section 4.6).
- 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 past arterial thromboembolic disease (e.g. cerebrovascular accident, myocardial infarction).
- Endometriosis.
- Porphyria.
- Patients known with inherited genetic mutations: BRCA 1 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 estrogen and/or progesterone/progestogen containing medicines irrespective of the indication, dosage formulation and route of administration.

4.4 Special warnings and precautions for use

Before starting, and periodically during EVOREL therapy, it is recommended that the patient be given a thorough physical and gynaecological examination. A complete medical and family history of venous or arterial thrombophlebitis or thromboembolic disorders should be taken. Repeated breakthrough bleeding, unexpected vaginal bleeding and changes noticed during breast examination require further evaluation.

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

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 estrogen-dependent tumours, e.g. first degree relative with breast cancer.
- Hypertension.
- Liver disorders (e.g. liver adenoma).
- Diabetes mellitus.
- Cholelithiasis.
- Migraine or severe headache.
- Systemic lupus erythematosus.
- A history of endometrial hyperplasia (see below).
- Epilepsy.
- Mastopathy.
- Otosclerosis.
- Dubin-Johnson syndrome.
- Rotor syndrome

Conditions which require monitoring while on estrogen therapy:

- Estrogens such as in EVOREL 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 with estrogen therapy such as EVOREL 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.

Endometrial hyperplasia

The risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods to women with an intact uterus.

Estrogen-only therapy in women with a uterus has been estimated to increase the risk of endometrial cancer with effects persisting for several years after estrogen is stopped.

To reduce, this risk, it is recommended that estrogen therapy is combined with a progestogen for 12 to 14 days per cycle in non-hysterectomised women.

Such a sequential estrogen/estrogen + progestogen regimen results in cyclic bleeding in the majority of women.

Women with an intact uterus who cannot tolerate or use a progestogen, should not use EVOREL.

Breakthrough bleeding and spotting may occur. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Unopposed estrogen stimulation such as EVOREL may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, a progestogen should be used concomitantly in postmenopausal women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

For patches > 50 µg/day, the addition of progestogens have not been demonstrated to protect against endometrial changes.

Breast cancer

EVOREL contains estrogen 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 estrogen-progestogen than estrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment.

The relative risk (RR) to develop breast cancer for estrogen-progestogen preparations was 1,60 at 1 – 4 years and RR = 2,08 at 5 – 14 years, while that for estrogen 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 should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. Mammography evaluations should be done on patient age, risk factors and prior mammogram results.

Combined estrogen progestogen 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 estrogen-progestogen for HRT that becomes apparent after about 3 years.

Estrogen-only therapy:
The WHI trial found no increase in the risk of breast cancer in hysterectomised women using estrogen-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 estrogen-progestogen 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 estrogen-only HRT products such as EVOREL in hysterectomised women has been associated with an increased risk of ovarian cancer.

Venous thromboembolism
Hormone replacement therapy (HRT) is associated with a higher 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.

Patients with a personal or a 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 initiated, use of EVOREL in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment should not use EVOREL.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. Scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, EVOREL treatment should be discontinued well ahead of surgery, if possible. Treatment should not be restarted until after the woman is completely mobilised.

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

Coronary artery disease (CAD)

Estrogen-only therapy:

Randomised controlled data found no protective effect in hysterectomised women of estrogen-only therapy for the risk of CAD.

Combined estrogen progestogen therapy:

The relative risk of CAD during use of combined estrogen-progestogen HRT is increased.

Stroke

Combined estrogen-progestogen and estrogen-only therapy such as EVOREL are associated with an up to 1,5-fold increase in risk of ischaemic stroke.

Dementia

HRT use does not improve cognitive function. There is evidence of increased risk of dementia in women who start using continuous combined or estrogen-only HRT such as EVOREL.

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. There is some evidence that use of estrogen 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.

Other Conditions

EVOREL is not to be used as contraception.

Keep EVOREL away from children.

4.5 Interactions with other medicines and other forms of interaction

Medicines with a high potential for liver enzyme induction, (e.g. barbiturates, hydantoin, carbamazepine, meprobamate, phenylbutazone, rifampicin, rifabutin, bosentan and certain non-nucleoside reverse inhibitors used in HIV treatments (e.g. nevirapine and efavirenz)) may interfere with the actions of EVOREL and decrease the efficacy of EVOREL.

Ritonavir and nelfinavir, although known as strong inhibitors of the cytochrome P450 isoenzymes, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Medicine metabolism may be affected by St. John's wort preparations (*Hypericum perforatum*), which induce certain cytochrome P450 isoenzymes in the liver (e.g. CYP3A4) as well as P-glycoprotein.

The induction of the P450 isoenzymes may reduce plasma concentrations of the estrogen component of EVOREL possibly resulting in a decrease in therapeutic effects and increased vaginal bleeding.

EVOREL has 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 medicines together.

Therefore, dosage adjustment of lamotrigine may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of EVOREL is contraindicated in pregnancy (see section 4.3).

If pregnancy occurs while using EVOREL, treatment should be withdrawn immediately.

Breastfeeding

The use of EVOREL is contraindicated during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

No information available.

4.8 Undesirable effects

Tabulated list of adverse reactions

Clinical Trial Data

Table 1: Adverse Reactions Reported by ≥ 1 % of EVOREL treated Subjects and With an Incidence Greater Than in Placebo-treated Subjects in 1 Double-blind, Placebo-Controlled Clinical Trial of EVOREL in 102 women:

System/Organ Class	***EVOREL %*** ***(N = 102)***	***Placebo %*** ***(N = 52)***
Infections and Infestations		
Genital candidiasis	*8,8*	*0*
Immune System Disorders		
Hypersensitivity	*2,9*	*1,9*
Nervous System Disorders		
Headache	*20,6*	*19,2*
Dizziness	*1,0*	*0*
Cardiac Disorders		
Palpitations	*1,0*	*0*
Gastrointestinal Disorders		
Flatulence	*4,9*	*0*
Diarrhoea	*1,0*	*0*

Skin and Subcutaneous Tissue Disorders		
Pruritus	*3,9*	*1,9*
Rash	*2,9*	*0*
Musculoskeletal and Connective Tissue Disorders		
Myalgia	*5,9*	*0*
Arthralgia	*2,0*	*0*
Reproductive System and Breast Disorders		
Breast pain	*12,7*	*3,9*
Metrorrhagia	*6,9*	*1,9*
Dysmenorrhoea	*2,9*	*0*
General Disorders and Administration Site Conditions		
Pain	*7,8*	*3,9*
Peripheral oedema	*5,9*	*1,9*
Generalised oedema	*3,9*	*1,9*
Oedema	*2,9*	*0*
Investigations		
Increased weight	*3,9*	*0*

Adverse drug reactions not reported in Table 1 that were reported by ≥ 1 % of EVOREL treated subjects (N = 2 584) in 15 clinical trials of EVOREL are shown in Table 2.

Table 2: Adverse Reactions Reported by ≥ 1 % of EVOREL treated Subjects in 15 Clinical Trials of EVOREL:

System/Organ Class	***EVOREL %*** ***(N = 2 584)***
Gastrointestinal Disorders	
Nausea	*2,4*
Abdominal pain	*1,8*
General Disorders and Administration Site Conditions	
*Application site rash**	*20,8 #*
*Application site pruritus**	*19,8 #*
*Application site erythema**	*8,5 #*
Application site reaction	*3,3*
*Application site oedema**	*1,6 #*

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

[#] *Percentages based on N = 1 739 in 8 clinical trials of EVOREL*

Adverse Drug Reactions reported by < 1 % of EVOREL treated subjects (N = 2 584) in the above clinical trial dataset are shown in Table 3.

Table 3: Adverse Drug Reactions Reported by < 1 % of EVOREL treated Subjects in 15 Clinical Trials of EVOREL:

Neoplasms benign, malignant and unspecified (Incl. cysts and polyps)	*Breast cancer*
Nervous system disorders	*Epilepsy*
Vascular disorders	*Arterial or venous thrombosis*

Post-marketing Data

Adverse reactions first identified during post-marketing experience with EVOREL are included in Table 4:

Table 4: Adverse Reactions Identified during Post-Marketing experience with EVOREL:

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	*Endometrial cancer*
Psychiatric Disorders	*Depressed mood* *Severe depression with a higher risk of suicidal thoughts/behavior and suicide*
Nervous System Disorders	*Cerebrovascular accident, migraine*
Cardiac Disorders	*Myocardial infarction*
Vascular disorders	*Deep vein thrombosis*
Respiratory, Thoracic and Mediastinal Disorders	*Pulmonary embolism*
Gastrointestinal Disorders	*Abdominal distension*
Hepatobiliary Disorders	*Cholelithiasis*
Skin and Subcutaneous Tissue Disorders	*Angioedema*
Reproductive System and Breast Disorders	*Breast enlargement*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers

are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms of overdose may include breast pain or tenderness, nausea, breakthrough bleeding, abdominal cramps and/or bloating. Removing the patch can reverse these symptoms. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.8.1 Estrogens.

Mechanism of action

EVOREL contains estradiol hemihydrates (17β-estradiol) which is a synthetically prepared estrogen.

Transdermal Delivery Systems deliver the hormone 17β-estradiol into the systemic circulation. 17β-estradiol, as in EVOREL provides a constant, controlled release of hormone for several days. The 17β-estradiol does not undergo first-pass liver metabolism.

Estrogens are derived by aromatisation of the A-ring mainly in the follicle apparatus in the ovary. Estradiol is the main estrogen of the ovary.

The molecular mechanism of estradiol action in the target organ estrogen receptor sites follows the known mechanism of steroid-hormone action. Estradiol binds to the intracellular receptors. An estradiol-receptor complex is formed and various metabolic changes are induced, which leads to tissue differentiation and growth.

Pharmacodynamic effects

The estradiol/estrone ratio in the plasma of post-menopausal women is between 0,2 and 0,5 which increases after transdermal application of estradiol to approximately 1 (normal pre-menopausal levels, early follicular phase).

5.2 Pharmacokinetic properties

Absorption and Distribution

Serum estradiol concentrations achieved in postmenopausal women following application of EVOREL are directly proportional to the size (dose) of the patches.

Concentrations, averaged over an entire 4-day application period were approximately 23; 44; 71 and 101 pg/ml above baseline for EVOREL 25; 50; 75 and 100.

Forty-eight hours after removal of the patch, estradiol serum concentration returns to the baseline.

Biotransformation

Estradiol's most important metabolites are estriol/estrone and conjugates (glucuronide and sulphate) which are far less active than estradiol and undergo enterohepatic recirculation. Overall, 60 - 80 % of the estrogens are excreted via the urine and 10 % via the faeces.

Elimination

The elimination half-life of the estradiol in the plasma is approximately 1 hour.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acrylate vinylacetate- copolymer (adhesive)
Guar gum (absorbent)
Polyethylene terephathalate foil (backing film)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.
Do not freeze.

6.5 Nature and contents of container

Cartons containing one or more patches. Each patch is sealed in a pouch.

6.6 Special precautions for disposal and other handling

Once removed, the patch should be folded and disposed of in the household waste (do not flush down the toilet).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
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Erand Gardens
Midrand, 1685
South Africa
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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