SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

EVOREL® CONTI, 50 µg, 170 µg, Patches

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each EVOREL CONTI patch contains 3,1 mg estradiol, formulated as 3,2 mg of estradiol hemihydrate and 9,82 mg norethisterone, formulated as 11,2 mg of norethisterone acetate. The patch delivers 50 µg of estradiol and 170 µg of norethisterone acetate per 24 hours.

EVOREL CONTI contains no sugar.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

EVOREL CONTI is a matrix type transdermal patches.

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Posology

Adults

EVOREL CONTI should be applied twice weekly, without interruption to the trunk below the waist.

EVOREL CONTI should not be continued for longer than 5 years.

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

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 CONTI in the elderly (> 65 years old).

Method of administration

Transdermal use.

Directions for use/handling

The EVOREL CONTI 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, a new patch should be applied immediately. However, the usual day of changing patches should be maintained.

It is not necessary to remove the patch during bathing or showering. It is recommended, however, that the patch be removed prior to a sauna bath, and that a new patch is applied immediately thereafter.

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.

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

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

4.3 Contraindications

- Known hypersensitivity to estradiol, norethisterone acetate or any other component of this product 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.
- Pregnancy and 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).
- 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

Prior to commencing, and periodically during therapy, 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 CONTI, 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
- 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 CONTI therapy:

- Estrogens such as in EVOREL CONTI 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 CONTI 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 CONTI 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 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 CONTI 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 CONTI 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 CONTI.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma surgery. Scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery EVOREL CONTI 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 mobilised.

If VTE develops after initiating therapy, EVOREL CONTI 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)

Estrogen only:

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

Combined estrogen progestogen therapy such as EVOREL CONTI*:*

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

Stroke

There is an increased risk of stroke in healthy women during treatment with HRT.

Combined estrogen progestogen and estrogen only therapy are associated with an increased 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 such as EVOREL CONTI or estrogen-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 CONTI. 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 CONTI.

EVOREL CONTI is not to be used as contraception.

The EVOREL CONTI should be kept away from children.

4.5 Interactions with other medicines and other forms of interaction

Medicines which induce microsomal liver enzyme activity may alter estrogen and progestogen metabolism and reduce the therapeutic effect of EVOREL CONTI.

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 estrogen component of EVOREL CONTI 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 CONTI, which could result in a diminished protective effect against estrogen induced endometrial hyperplasia.

Estrogen-containing oral contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine when co administered due to induction of lamotrigine glucuronidation.

This may reduce seizure control. Although the potential interaction between EVOREL CONTI 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 CONTI is contraindicated in pregnancy (see section 4.3).

If pregnancy occurs during medication with EVOREL CONTI, treatment should be withdrawn immediately.

Breastfeeding

The use of EVOREL CONTI 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 summary of adverse reactions

Clinical Trial Data

The safety of EVOREL CONTI was evaluated in 196 subjects in 3 clinical trials (including 2 active-controlled trials and 1 single arm trial). Adverse drug reactions (ADRs) reported for ≥ 1 % of EVOREL CONTI treated subjects are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥ 1 % of EVOREL CONTI-treated Subjects in 3 Clinical Trials of EVOREL CONTI

System/Organ Class	**EVOREL CONTI % (N=196)**
Immune System Disorders	
Hypersensitivity	1,0
Psychiatric Disorders	
Depression	2,6
Nervousness	2,6
Anxiety	1,0
Insomnia	1,0
Nervous System Disorders	
Headache	8,2
Paraesthesia	1,0
Cardiac Disorders	
Palpitations	2,6
Vascular Disorders	
Hypertension	3,6
Vasodilation	2,6

Varicose vein	1,0
Gastrointestinal Disorders	
Abdominal pain	4,1
Nausea	2,6
Skin and Subcutaneous Tissue Disorders	
Rash erythematous	1,0
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	3,1
Back pain	2,6
Reproductive System and Breast Disorders	
Menstrual disorder	7,1
Breast pain	5,1
Metrorrhagia	3,6
Genital discharge	1,5
Cervical polyp	1,0
Dysmenorrhoea	1,0
Endometrial hyperplasia	1,0
Menorrhagia	1,0
General Disorders and Administration Site Conditions	
Application site reaction	11,7
Oedema	4,1
Fatigue	3,1
Pain	1,0
Investigations	
Increased weight	2,0

ADRs reported by < 1 % of treated subjects (N=196) in the above clinical trial dataset are shown in Table 2.

Table 2. Adverse Drug Reactions Reported by < 1 % of treated Subjects in 3 Clinical Trials with an estradiol and norethisterone patch

System/Organ Class	***Adverse Reaction***
Psychiatric Disorders	*Decreased libido*
Skin and Subcutaneous Tissue Disorders	*Pruritus*
General Disorders and Administration Site Conditions	*Generalised oedema*

Additional ADRs reported in clinical trials with an estradiol 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	***Adverse Reaction***
Infections and Infestations	*Genital candidiasis*
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	*Breast cancer*
Nervous System Disorders	*Dizziness, epilepsy*
Vascular Disorders	*Venous & Arterial Thrombosis & 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,** *Peripheral oedema,* *Pain*

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

Post marketing Data

Table 4. Adverse Drug Reactions Identified During Post Marketing Experience with EVOREL CONTI

Infections and Infestations	*Candidiasis*
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	*Breast neoplasms, endometrial cancer*
Psychiatric Disorders	*Mood swings* *Severe depression with a higher risk of suicidal thoughts/behavior and suicide*
Nervous System Disorders	*Cerebrovascular accident, dizziness, migraine*

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*
Reproductive System and Breast Disorders	*Breast enlargement*
General Disorders and Administration Site Conditions	*Application site erythema, Application site pruritus, Application site rash*

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 of EVOREL CONTI therapy may include nausea, break-through bleeding, breast tenderness, abdominal cramps and/or bloating. These symptoms can be reversed by removing the EVOREL CONTI.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.8.2 Progesterones with estrogens

EVOREL CONTI contains estradiol hemihydrates (17β – estradiol), which is a synthetically prepared estrogen and norethisterone acetate, the acetate ester or norethisterone, a synthetic progestin.

Estradiol (E_2)

After application to the skin the patch delivers 17ß-estradiol, a physiological hormone, transdermally into the systemic circulation and consequently, the 17ß-estradiol does not undergo first pass liver metabolism. In postmenopausal women, EVOREL CONTI raise the estradiol concentrations to levels similar to those in the early follicular phase and maintain these levels over the application period of 3 – 4 days.

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

Norethisterone acetate (NETA)

Norethisterone acetate, used in the EVOREL CONTI, is hydrolysed to norethisterone, a synthetic 19-nortestosterone derivative of the 13-methyl gonane group with potent progestational activity.

Transdermal norethisterone acetate administration prevents estrogen related endometrial proliferation.

5.2 Pharmacokinetic properties

Estradiol

Estradiol 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 estradiol. Estradiol is promptly eliminated from the systemic circulation.

Estradiol is metabolised principally into the less pharmacologically active estrone and its conjugates.

Estradiol, estrone and estrone sulphate are interconverted to each other and are excreted in urine as glucuronides and sulphates. The skin metabolises estradiol only to a small extent.

Norethisterone

Norethisterone acetate is hydrolysed to the active progestogen, norethisterone. Transdermal delivery of norethisterone acetate produces a sustained 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, ß 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

Estradiol: In a single and multiple application study in post-menopausal women, serum estradiol concentrations increased rapidly from pre-treatment levels (about 5 pg/ml) after application of an EVOREL CONTI.

At four hours after application, the mean serum estradiol concentration was about 19 pg/ml. A mean peak serum estradiol concentration of about 41 pg/ml above the pre-treatment level was observed at about 23 hours following application.

Serum estradiol 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 application of the patch resulted in little or no accumulation of estradiol in the systemic circulation.

During use of EVOREL CONTI, the 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.

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 concentrations was observed following multiple application of the patch.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adhesive: acrylate vinylacetate copolymer
Guar gum
Backing film: polyethylene terephthalate foil
Release liner: siliconised polyethylene terephthalate foil which is removed before application.

6.2 Incompatibilities

No data available.

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 eight EVOREL CONTI patches in foil lined pouches.
The pouch comprises a 4 layer laminate including an aluminium barrier and paper exterior surface.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

31/21.8.2/0537

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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