SCHEDULING STATUS

S4

EVOREL® 25; 50; 75 and 100, 25 µg; 50 µg; 75 µg; 100 µg Patches

Estradiol

Read all of this leaflet carefully before you start using EVOREL

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- EVOREL 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.

What is in this leaflet

1. What EVOREL is and what it is used for
2. What you need to know before you use EVOREL
3. How to use EVOREL
4. Possible side effects
5. How to store EVOREL
6. Contents of the pack and other information

1. What EVOREL is and what it is used for

EVOREL patches contain a synthetic estrogen called estradiol. It belongs to a group of medicines called hormone replacement therapy (HRT).

The patches come in 4 different sizes: EVOREL 25, EVOREL 50, EVOREL 75, and EVOREL 100.

What EVOREL is used for

EVOREL patches are used for hormone replacement therapy (HRT) in the treatment of symptoms of the menopause.

EVOREL at a minimum dose of EVOREL 50, can also be used for the prevention and management of osteoporosis in post-menopausal women.

How EVOREL patches work

The EVOREL patch replaces the natural estrogen that is normally released by the ovaries. It does this by passing estrogen from the patch into the body through the skin. The active levels of estrogen in the body are reached about 4 hours after the patch is applied to the skin and last for 3 to 4 days after which the patch must be changed.

EVOREL should not be used by children.

EVOREL should not be used for contraception.

2. What you need to know before you use EVOREL

Do not use EVOREL if:

- You are allergic (hypersensitive) to estradiol or any of the ingredients in EVOREL patches (see section 6: "*What EVOREL contains*" below).
- You had, have or suspect that you have breast cancer.
- You have a family history of breast cancer.
- You have or suspect other cancers known to be sensitive to estrogens (e.g. endometrial cancer) or pre-malignant tumours (e.g. untreated atypical endometrial hyperplasia).
- You have undiagnosed genital bleeding.
- You are pregnant or breastfeeding.
- You have acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal.
- You have or have had blood clots (thrombosis) or inflammation of veins (thrombophlebitis) or alternatively, a family history thereof.
- You have a previous or current venous thromboembolism (blood clots of deep veins in legs, clots in the lungs).
- You have active or recent past arterial thromboembolic disease (e.g. stroke, heart attack).
- Porphyria.
- You have depression, which is not well controlled with treatment.
- You have had depression with previous use of estrogen containing medicines.

Warnings and precautions

Medical check-ups

- It is important that you have full and thorough physical and gynaecological examinations and that your own family's medical histories regarding thrombosis (blood clots) are taken before you start any Hormone Replacement Therapy (HRT).

- Repeated breakthrough bleeding, unexpected vaginal bleeding and changes noticed during breast examination require further evaluation.
- You should receive regular full medical examinations whilst using EVOREL.

Take special care with EVOREL. Before you use EVOREL, 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).
- You are on treatment for depression.
- You have had depression with previous use of estrogen and/or progesterone/progestogen containing medicines.
- You have a substance abuse problem.
- You have underlying psychiatric disorder such as post-traumatic stress disorder or bipolar disorder.
- You have a family history of mental disorders.
- You have a history of physical or sexual abuse.

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, you should be closely supervised by your doctor as these conditions may recur or be aggravated during treatment with EVOREL, in particular:

- Leiomyoma (womb fibroids) or endometriosis.
- Risk factors for blood clotting.
- Risk factors for estrogen-dependent tumours, e.g. first degree relative with breast cancer.
- High blood pressure.
- Liver disorders (including benign tumours of liver cells).
- Diabetes mellitus.
- Gall stones.
- Migraine or severe headache.
- Systemic lupus erythematosus (lupus).
- A history of endometrial overgrowth (endometriosis).
- Epilepsy.

- Loss of hearing or ringing in the ears.
- Breast tissue disease.

Conditions which require monitoring by your doctor while on estrogen therapy:

- EVOREL may cause fluid retention. Heart or kidney abnormalities should be carefully observed.
- Disturbances of liver function.
- History of yellowing of the skin and or mucous membranes (jaundice).
- Pre-existing elevated blood fats, including triglycerides.

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Yellowing of skin (jaundice) or deterioration in liver function.
- Increase in blood pressure.
- New onset of migraine-type headache.
- Pregnancy.
- Epilepsy.

EVOREL 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, you must perform monthly breast self-examinations. Your doctor will advise you on when to report for breast examinations and any appropriate investigations.

There is some evidence that HRT, such as EVOREL increases the risk of breast cancer in postmenopausal women receiving long-term HRT. You should discuss with your doctor for how long you should receive EVOREL treatment. If you have taken EVOREL for 5 years you should discuss with your doctor whether you should receive further HRT treatment.

EVOREL and endometrial (womb) / ovarian cancer

If you still have a womb (i.e. have not had a hysterectomy), taking EVOREL may increase the risk of overgrowth and cancer of the womb lining. You should discuss this with your doctor who could prescribe another hormone, progestogen, to take with the EVOREL since EVOREL in combination with a progestogen (for at least 12-14 days per cycle in non-hysterectomised women) reduces the risk.

Long term use of estrogen-only HRT products such as EVOREL has been associated with an increased risk of ovarian cancer.

EVOREL and heart disease / stroke / blood clots
EVOREL does not protect against heart disease.
Estrogen-only therapy such as EVOREL is associated with an increase in the risk of stroke.
If you have had a blood clot in the leg or lung, a stroke or a heart attack or are immobile for any reason, such as after an operation, your doctor should decide on this and check you regularly if you do use it. If, while using EVOREL, 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 should be contacted immediately.

Depressed mood, depression and the risk of suicidality
Estrogen containing medicines including EVOREL, 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.

Dementia
There is some evidence of increased risk of deterioration of mental function (dementia) in women who start using continuous combined or estrogen-only HRT such as EVOREL.

EVOREL should not be used for contraception.

Children and adolescents
EVOREL should not be used by children.

Other medicines and EVOREL

Always tell your health care provider if you are taking any other medicine. (This includes all complementary or traditional medicines.)

Some medicines can alter the way EVOREL works, such as barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone, rifampicin, rifabutin, bosentan, St. John's wort preparations (*Hypericum perforatum*) and certain non-nucleoside reverse transcriptase inhibitors, such as nevirapine and efavirenz, used in the treatment of HIV/AIDS.

Ritonavir and nelfinavir, used in the treatment of HIV/AIDS, may increase the metabolism of EVOREL and reduce plasma concentrations of estrogen. Use of EVOREL with ritonavir and nelfinavir may result in a decrease in the effects and in unscheduled bleeding.

EVOREL may interfere with the plasma concentration of the anti-epileptic medicine lamotrigine. This may have an effect on the control of your seizures. If you have epilepsy and are taking medicines for this condition, inform your doctor as the dosage of your anti-epileptic medicine may need to be adjusted.

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before using EVOREL.

You should not use EVOREL during pregnancy. You should not breastfeed when using EVOREL.

If you fall pregnant whilst using EVOREL, stop treatment immediately and tell your doctor.

Driving and using machines

There is no information about whether EVOREL affects your ability to drive or use machines.

It is not always possible to predict to what extent EVOREL may interfere with your daily activities. Do not engage in above activities until you are aware of the measure to which EVOREL affects you.

3. How to use EVOREL

Do not share medicines prescribed for you with any other person.

Always use EVOREL exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How should you use EVOREL patches?

EVOREL patches are available in 4 different sizes: EVOREL 25, EVOREL 50, EVOREL 75 and EVOREL 100. These contain different amounts of the estrogen hormone estradiol. Your doctor will choose which size is suitable for you to use.

HRT treatment should be continued for no longer than 5 years.

The following instructions apply to all 4 sizes of EVOREL patches:

When to use the patch

There are enough hormones in each patch to last for several days but to ensure a steady supply to the body; 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 your two days from the following table, starting from the first day of use:

If you put your first patch on:

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 remember your "two patch change" days, mark them as shown:

Mon Tues Wed Thur Fri Sat Sun

Thur Fri Sat Sun Mon Tues Wed

How to put the patch 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 EVOREL 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 silver 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.

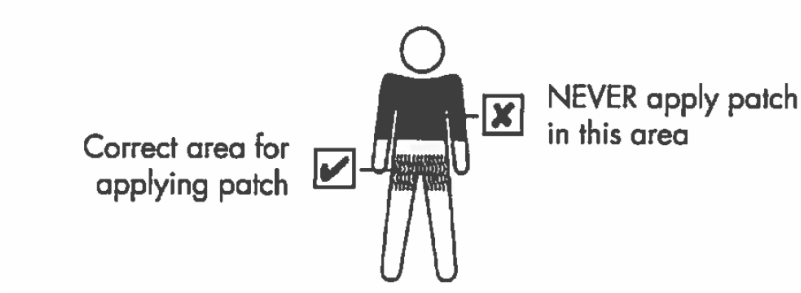


(f) You may use soap and water to help remove any gum/glue, which may remain on your skin after patch removal.

Where to place the EVOREL Patch

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.



Just apply a new patch and keep to your original "patch change" days. If you have just had a bath or shower, wait until your skin cools before applying a new patch.

Can I wash, bath or shower as normal?

YES, but do not scrub too hard in case you loosen the edges of the patch. It is recommended, however, that the patch be removed prior to a sauna bath, and that a new patch is applied immediately thereafter.

Can I go swimming with the patch on?

YES, the patch will not be affected.



Can I exercise or play sports?

YES, 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 are unlikely. However, 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 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 consult your doctor.

If you use more EVOREL than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

Overdosage with the patch is unlikely. Effects of too much estrogen can be reversed simply by removal of the patch. Your doctor may decide to change you to a different size of EVOREL patch. The most common symptoms of estrogen overdose are breast tenderness, nausea and irregular bleeding.

If you forget to use EVOREL

If you 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 breakthrough bleeding and spotting.

4. Possible side effects

EVOREL can have side effects.

Not all side effects reported for EVOREL are included in this leaflet. Should your general health worsen or if you experience any untoward effect while using EVOREL, please consult your health care provider for advice.

Side effects may include the following:

Frequent:

- Genital yeast infections
- Allergic reactions
- Headache
- Dizziness
- Abnormal heart beat
- Excess amount of gas in stomach
- Loose watery stools
- Itching
- Rash
- Muscle pain
- Joint pain
- Breast pain
- Breakthrough bleeding or spotting
- Painful menstruation
- Pain
- Swelling (whole body or legs)
- Increased weight
- Feeling sick
- Abdominal pain
- Application site rash
- Application site itching
- Application site redness
- Application site reaction
- Application site swelling

Less frequent

- Breast cancer

- Epilepsy
- Blood clots in veins.
- Cancer of womb lining
- Depressed mood
- Suicidal thoughts/behaviour and suicide
- Stroke, migraine
- Heart attack
- Clots in the deep veins, especially of lower leg
- Blood clot in the lungs
- Bloating of the stomach
- Gall stones
- Swelling below surface of skin
- Breast enlargement

If you react to the patch itself with skin rashes or irritation, remove the patch and ask your doctor for advice.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist. You can also report side effects 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. By reporting side effects, you can help provide more information on the safety of EVOREL.

5. How to store EVOREL

- Store all medicines out of reach of children.
- EVOREL should be stored at or below 25 °C.
- Do not freeze.
- Keep used and unused patches out of reach of children and pets. The used patch should be folded and put 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

Return all unused medicine to your pharmacist. Do not dispose of unused medicine in drains or sewerage systems (e.g., toilets).

6. Contents of the pack and other information

What EVOREL contains

The active substance is estradiol. The patches come in 4 different sizes: EVOREL 25, EVOREL 50, EVOREL 75, and EVOREL 100. The patches contain 1,6 mg, 3,2 mg, 4,8 mg and 6,4 mg of estradiol hemihydrate, respectively.

EVOREL 25, EVOREL 50, EVOREL 75 and EVOREL 100 patches contain the following inactive ingredients: Acrylate-vinylacetate copolymer (adhesive), guar gum (absorbent) and polyethylene terephthalate foil (backing film).

What EVOREL looks like and contents of the pack

EVOREL patches are square shaped with rounded corners, transparent patches with a self-adhesive backing, which can be stuck to the skin.

EVOREL 25 has a surface area of 8 cm^2. The outside of the backing film is marked CE25 on the distal side.

EVOREL 50 has a surface area of 16 cm^2. The outside of the backing film is marked CE50 on the distal side.

EVOREL 75 has a surface area of 24 cm^2. The outside of the backing film is marked CE75 on the distal side.

EVOREL 100 has a surface area of 32 cm^2. The outside of the backing film is marked CE100 on the distal side.

In each patch the estradiol is spread evenly in the adhesive and this passes slowly through the skin into the body.

Holder of Certificate of Registration

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