

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986
The medicine is dispensed with a doctor's prescription only

Evorel 50, Transdermal Patch

The active ingredient and its quantity per dosage unit:

estradiol (as hemihydrate) 3.2 mg
Releases 50 mcg estradiol per day

Inactive and allergenic ingredients in the preparation – see section 6 “Further Information”.

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

For the treatment of effects associated with estrogen deficiency in women before or after the age of cessation of menstruation, during menopause (resulting from a natural process or following surgical removal of the ovaries), such as: hot flushes, insomnia, vaginal and genital changes, mood changes, and bone loss (calcium depletion) which can lead to osteoporosis. In women who have not undergone a hysterectomy, estrogen therapy must be supplemented with a sequential gestogen therapy.

Therapeutic group: Estrogens.

Evorel 50 is a non-contraceptive hormone replacement therapy (HRT).

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the additional ingredients contained in the medicine (as listed in section 6 “Further Information”)
- You have, have ever had, or are suspected of having breast cancer
- You have, have ever had, or are suspected of having a cancerous tumor that is made worse by estrogens (such as endometrial cancer)
- You have a thickening of the lining of the womb which has not been treated
- You have unexplained vaginal bleeding
- You have ever had blood clots in the veins (thrombosis) or a blood clot that has traveled to the lungs (pulmonary embolism)
- You have problems with your blood which may increase the likelihood of developing a blood clot (thrombosis) (such as protein C, protein S or antithrombin deficiency)
- You have, or have ever had, a liver disease and your liver function tests have not yet returned to normal
- You have ever had blocked arteries that led to angina pectoris or a heart attack that resulted in a stroke
- You have a blood problem called porphyria

Special warnings regarding use of the medicine

Medical check-ups

Before taking hormone replacement therapy such as Evorel 50, the doctor should ask you about your and your family's medical history. The doctor may decide to perform a physical examination of the breasts or abdomen, and may do an internal examination. The doctor will only do so if it is necessary, or if you have any special concerns.

Once you have started using the hormone replacement therapy, you should meet with your doctor for periodic medical check-ups (at least once a year). At these check-ups, your doctor may discuss the benefits and risks of continuing treatment.

Make sure that you:

- Undergo periodic breast examinations and cervical smear tests
- Perform breast examinations to identify changes such as dimpling of the skin, changes in the nipple, or lumps that can be seen or felt

Tell the doctor if you have ever had any of the following conditions. You may need periodic medical check-ups more often

- A problem caused by growth of the womb lining
 - Inside the womb – fibrosis
 - Outside the womb – endometriosis
 - Thickening of the lining of the womb (endometrial hyperplasia)
- Increased risk of blood clots (see “Blood clots” section below)
- A family history of increased risk of cancers related to estrogens (see “Breast cancer” section below)
- Hypertension. The doctor may tell you to stop using Evorel 50 if your blood pressure rises
- Diabetes
- Gallstones
- Migraine or severe headaches
- Systemic lupus erythematosus (SLE). This is an allergic condition that causes joint pain, skin rash and fever
- Epilepsy
- Asthma
- A disease affecting the eardrum (otosclerosis)
- Liver, heart or kidney problems
- High level of triglycerides (fats) in the blood that may raise the risk of pancreatitis (which causes severe pain in the abdomen and back)
- Breast problems
- History of sudden swelling of the face or throat, which may cause difficulty in swallowing or breathing, rapid swelling of the hands and feet, and stomach cramps

You may still be able continue treatment with Evorel 50, but you should first discuss this with the doctor. Please inform the doctor if these medical conditions recur or get worse during the course of treatment with Evorel 50.

The risk of use of hormone replacement therapy in cases of premature menopause is different.

Consult with the doctor regarding the risks.

Smoking

If you smoke, do not use the medicine without consulting the doctor. It is recommended that you quit smoking while using Evorel 50. If you are unable to quit smoking and you are over the age of 35, consult a doctor. Smoking is a risk factor of venous thromboembolism (VTE).

Children and adolescents

The medicine is not intended for use in children.

Other conditions

If you have brown patches on your face or body (chloasma) or have suffered from such patches in the past, you may need to avoid exposure to the sun or tanning beds (these patches may not completely disappear).

Operations or check-ups

Please inform the doctor if you are going to have surgery. You may need to stop using Evorel 50 4 to 6 weeks before the surgery to reduce the risk of a blood clot. The doctor will tell you when you can resume taking Evorel 50.

If you perform a blood or urine test in a hospital or at the family doctor, please tell them that you are taking Evorel 50. This is because Evorel 50 may affect the results of the tests.

Drug interactions

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially if you are taking:

- Medicines for epilepsy such as: phenobarbital, phenytoin or carbamazepine.
- Certain medicines for treatment of infections such as: rifampicin, rifabutin, nevirapine, efavirenz, ritonavir or nelfinavir.
- Bosentan – a medicine for hypertension in the blood vessels of the lungs.
- St. John's wort – for depression.

Taking these medicines with Evorel 50 may impair the efficacy of Evorel 50, and you may therefore suffer from bleeding, like a period, when you are not expecting it.

- Lamotrigine – a medicine for epilepsy. Concomitant use of Evorel 50 and lamotrigine could affect the control of your epilepsy.

Pregnancy and breastfeeding

Do not use the medicine if you are pregnant, may be pregnant or might become pregnant. This is because Evorel 50 may affect the baby.

If you are pregnant, please contact the doctor immediately and remove the patch.

Do not use the preparation if you are breastfeeding.

Driving and use of machinery

There is no information about whether Evorel 50 affects your ability to drive or operate machinery. Please check to see how the medicine affects you before driving or using heavy tools or operating machinery.

Safety of hormone replacement therapy

In addition to the benefits, use of HRT bears some risks. Consider the following information before using or continue to use hormone replacement therapy.

Heart diseases

Hormone replacement therapy **is not recommended** for women who have had heart diseases recently. If you have ever had heart disease, discuss with the doctor whether or not you should use HRT.

Hormone replacement therapy will not help to prevent heart diseases.

Studies of hormone replacement therapy (containing both estrogen and progestogen) have shown that women are more likely to get a heart disease.

If you are experiencing **chest pain** that spreads to the arm and neck

- Refer to a doctor as soon as possible**
- Do not use hormone replacement therapy any more** until the doctor says you can

The chest pain may be indicative of heart disease.

Stroke

Studies suggest that hormone replacement therapy slightly increases the risk of getting a stroke.

Other things may increase the risk of stroke include:

- Getting older
- Hypertension
- Smoking
- Drinking too much alcohol
- An irregular heartbeat

If you are worried about any of the above-mentioned, or if you have had a stroke in the past, please talk to the doctor regarding use of these preparations.

How likely is a stroke?

Looking at women in their 50s, over 5 years, on average:

- 3 out of 1000 women not taking hormone replacement therapy are expected to have a stroke
- 4 out of 1000 women taking hormone replacement therapy are expected to have a stroke

Looking at women in their 60s, over 5 years, on average:

- 11 out of 1000 women not taking hormone replacement therapy are expected to have a stroke
- 15 out of 1000 women taking hormone replacement therapy are expected to have a stroke

If you suffer from unexplained **migraine-type headaches**

- Refer to a doctor as soon as possible**
- Do not use hormone replacement therapy any more** until the doctor says you can

These headaches may be an early warning sign of a stroke.

Blood clots

Hormone replacement therapy may increase the risk of formation of blood clots in the veins (DVT - deep vein thrombosis), especially during the first year of taking it. These blood clots are not always serious. However, if such a blood clot travels to the lungs, it can cause chest pain, breathlessness, collapse or even death. This condition is called pulmonary embolism (PE).

There is a higher likelihood of getting a blood clot:

- If you are overweight (BMI above 30 kg/m²)
- If you have had a blood clot in the past
- If you are taking a medicine containing an estrogen
- With increased age
- If you have cancer
- If you have just had a baby
- If one of your family members suffered from blood clots
- If you have had one or more miscarriages
- If you have a blood clotting problem because of which you are taking a medicine such as warfarin
- If you are immobile for a lengthy period of time because of surgery, injury or illness
- If you are due to go on a long journey, during which you will be immobile for some time
- If you have a rare illness called systemic lupus erythematosus (SLE)

If any of these conditions are relevant to you, please consult with the doctor before commencing use of the medicine.

How likely is a blood clot?

Looking at women in their 50s, over 5 years, on average:

- 3 out of 1000 women not taking hormone replacement therapy are expected to have a blood clot
- 7 out of 1000 women taking hormone replacement therapy are expected to have a blood clot

Looking at women in their 60s, over 5 years, on average:

- 8 out of 1000 women not taking hormone replacement therapy are expected to have a blood clot
- 17 out of 1000 women taking hormone replacement therapy are expected to have a blood clot

If you suffer from painful swelling in the legs, sudden chest pain or have difficulty breathing

- Refer to a doctor as soon as possible**
- Do not use hormone replacement therapy any more** until the doctor says you can

These may be signs of a blood clot.

Breast cancer

Evidence shows that taking combined estrogen-progestogen or estrogen-only hormone replacement therapy (HRT) increases the risk of breast cancer.

The extra risk depends on how long you use HRT. The additional risk becomes clear within 3 years of use. After stopping HRT, the extra risk will decrease with time, but the risk may persist for 10 years or more if you have used HRT for more than 5 years.

How likely is breast cancer?

- For women aged 50-54 who are not taking HRT, on average, 13-17 out of 1000 will be diagnosed with breast cancer over a 5-year period.
- For women aged 50 who start taking estrogen-only HRT for 5 years, there will be 16-17 cases in every 1000 users (i.e., an extra 0 to 3 cases).
- For women aged 50 who start taking estrogen-progestogen HRT for 5 years, there will be 21 cases in every 1000 users (i.e., an extra 4 to 8 cases).
- For women aged 50-59 who are not taking HRT, on average, 27 out of 1000 will be diagnosed with breast cancer over a 10-year period.
- For women aged 50 who start taking estrogen-only HRT for 10 years, there will be 34 cases in every 1000 users (i.e., an extra 7 cases)
- For women aged 50 who start taking estrogen-progestogen HRT for 10 years, there will be 48 cases in every 1000 users (i.e., an extra 21 cases).

If you notice any changes in your breast, such as:

- Dimpling of the skin
- Changes in the nipple
- Lumps that can be seen or felt

Make an appointment to see your doctor as soon as possible.

Endometrial cancer

Taking estrogen-only hormone replacement therapy for a long period of time may increase the risk of endometrial cancer. Taking progestogen in addition to estrogen helps to reduce the increased risk.

In most cases, if you have not undergone a hysterectomy, the doctor will prescribe progestogen in addition to estrogen. These may be prescribed separately, or as combined hormone replacement therapy.

If you have undergone a hysterectomy, the doctor will discuss with you whether you can safely take an estrogen preparation without progestogen.

If you have undergone a hysterectomy because of endometriosis (growth of the endometrium outside of the womb), any endometrium left in your body may be at risk of cancer. The doctor may prescribe hormone replacement therapy that includes progestogen in addition to estrogen.

Evorel 50 is an estrogen-only hormone replacement therapy.

How likely is endometrial cancer?

Looking at women aged 50 who have not undergone a hysterectomy, on average, over the coming 15 years:

- 5 out of 1000 women not taking hormone replacement therapy will suffer from endometrial cancer
- In women taking estrogen-only hormone replacement therapy, the number of women will be 2-12 times higher, depending on the dosage and duration of treatment.

Addition of progestogen to estrogen-only hormone replacement therapy substantially reduces the risk of endometrial cancer.

If you get breakthrough bleeding or spotting, it is usually nothing to worry about, especially during the first few months of taking hormone replacement therapy. But if the breakthrough bleeding or spotting:

- Carries on for more than the first few months
- Starts after you have been on hormone replacement therapy for a while
- Carries on even after you have stopped taking the hormone replacement therapy

Make an appointment to see the doctor as soon as possible. These may be signs that the endometrium has become thicker.

Ovarian cancer

Ovarian cancer is rare, much rarer than breast cancer.

There is a link between use of estrogen-only or combined HRTs and an increased risk of ovarian cancer.

The risk of ovarian cancer varies with age.

For example, 2 women in 2000 aged 50-54 who are not taking HRT will be diagnosed with ovarian cancer over a 5-year period.

For women who are taking HRT for 5 years, 3 women in 2000 will be diagnosed with ovarian cancer (i.e., 1 extra case).

Dementia

Evorel 50 and similar preparations will not stop memory loss (dementia). Women who start using medicines like Evorel 50 after the age of 65 may have a slightly higher risk of dementia.

3. HOW SHOULD THE MEDICINE BE USED?

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain regarding the dosage and treatment regimen of the medicine.

The dosage and treatment regimen will be determined by the doctor only. The usual dosage is generally: Change the patches twice a week. Start using a new Evorel 50 package immediately after finishing the previous package, so that you will not have a break in treatment between packs.

Do not exceed the recommended dose. Do not swallow. For external use only.

When to start Evorel 50 treatment

Treatment can be commenced at any time if:

- You have not used HRT before your menopause and no longer have menstrual periods.
- Your menstrual cycle is not regular and you are not pregnant.
- You are changing from an HRT preparation that does not give you a withdrawal bleed.

Put an Evorel 50 patch on within 5 days of the start of bleeding if:

- You are not currently using HRT and are still having regular periods.

Put an Evorel 50 patch on at the end of a treatment cycle or one week after you finish using another HRT preparation if:

- You are changing from an HRT preparation that caused you a withdrawal bleed.

If you are taking another type of HRT:

- The day you start treatment with Evorel 50 depends on the type of the other HRT. Please refer to a doctor if you are not sure which type of HRT preparation you are using.

Changing Evorel 50 patches

- Change the patches twice a week to give your body a steady supply of hormones. There is enough hormone in each patch to last for several days.
- Change the patch twice a week on the same two days. This will mean that one patch is used for three days and the next patch for four days.
- For example, if you applied your first patch on Monday, put on the second patch on Thursday. You can decide on your two changing days from the following table:

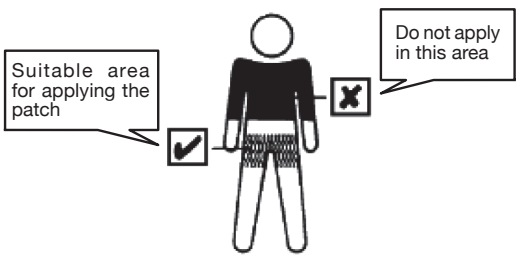
If you put your first patch on	Change to the next patch on	Change again on
Monday	→ Thursday	& Monday
Tuesday	→ Friday	& Tuesday
Wednesday	→ Saturday	& Wednesday
Thursday	→ Sunday	& Thursday
Friday	→ Monday	& Friday
Saturday	→ Tuesday	& Saturday
Sunday	→ Wednesday	& Sunday

To help you remember your two patch change days, mark them on the back of the package. They are written on the package like this:

MON/THUR	TUE/FRI	WED/SAT	THUR/SUN	FRI/MON	SAT/TUE	SUN/WED
----------	---------	---------	----------	---------	---------	---------

Where to apply the patches

- Apply the patch onto a hairless area of skin below the waistline. Most women prefer to wear the patch on the thigh or buttocks.
- Do not apply on or near the breasts.
- Do not apply on skin with cuts, spots or anywhere the skin is irritated.
- Do not apply cream, moisturizer or sprinkle talc before applying the patch.
- Do not apply a new patch in the same area where the previous patch was placed.
- The patch can be applied under clothing, in areas where the clothing is loose.
- Do not apply the patch under elastic or rubber bands.
- Apply the patch on clean, dry and cool skin immediately after removing the patch from the protective pouch.

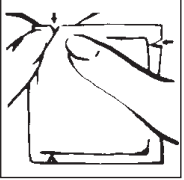


Applying a patch

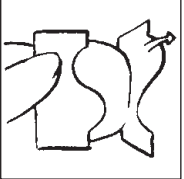
Do not use a patch if the protective pouch is already open.

Step 1: Open and Peel

- Use the notches as a guide, and tear along the 2 edges of the pouch. Remove the patch.



- Hold the patch with its cover (the aluminum-type foil) facing you, fold the patch gently and remove one part of the aluminum foil covering the patch. Avoid touching the sticky side of the patch – it may impair its adhesive properties.



Step 2: Apply and Press

- Apply the exposed half of the patch to your skin.
- Peel off the second half of the aluminum-type foil and press the second half of the patch onto the skin.



- Press the patch onto the skin using the palm of your hand to ensure that it is firmly stuck to the skin.



Removing a patch

- Peel the edges of the patch away from the skin and remove it by pulling gently.
- Fold the patch in half, so that the adhesive side is inward.
- Place the patch in a household waste bin, out of the reach of children and animals.
- Do not dispose of used patches in the toilet. After removing the patch, a little glue may remain on your skin. The glue will disappear with time. You may also use baby oil to remove the remnants of the glue.

If a patch falls off

Replace the patch that has fallen off with a new patch but keep to your original patch change days. If you have just had a shower or bath, wait until your skin cools before applying a new patch.

Talk to your doctor if you need more patches.

If you forget to change the patch

Change the patch as soon as you remember. The patch change days do not change. In this case, you may get some spotting or period-like bleeding during this time.

If you used a higher dosage of Evorel 50 than recommended

It is unlikely that you will get too much of the hormones in Evorel 50. The most common symptoms of having too much estrogen in your body are:

- Painful or tender breasts
- Nausea or vomiting
- Unexpected vaginal bleeding
- Stomach pain or bloating

These symptoms, which result from excess estrogen, are reversible upon removal of the patch. Consult the doctor or pharmacist before using another patch. The doctor may decide to change the treatment.

Contraception while using Evorel 50

The hormone levels in the preparation are too low to be used as a contraceptive.

Use a non-hormonal contraceptive method (such as a condom, diaphragm or ring) until your periods have completely stopped.

Everyday activities

- You can shower or take a bath as usual. Do not scrub the skin around the patch too hard, as this may loosen the edges of the patch.
- You can go swimming. The patch will not be affected by this activity.
- You can exercise. Do not apply the patch under tight clothing or elastic or rubber bands.
- You can sunbathe, but be sure to keep the patch under a garment, out of direct sunlight.

Adhere to the treatment as recommended by the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Evorel 50 may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Some of the side effects may be caused by progesterone taken at the same time.

The following diseases are reported more often in women taking HRT preparations, as compared to women not taking such preparations:

- Breast cancer
 - Abnormal growth or cancer of the lining of the womb
 - Ovarian cancer
 - Blood clots in the veins of the legs or lungs
 - Heart diseases
 - Stroke
 - Probable memory loss if HRT began over the age of 65
- For further information about these side effects, refer to section 2 in the leaflet.
- Take off the patch and refer to a doctor immediately if you notice or suspect any of the following conditions. You may need urgent medical treatment.**
- Sudden swelling of the face or throat which causes difficulty in swallowing or breathing. This may be a sign of an allergic reaction. This effect only happens in a small number of people
 - Blood clots (thrombosis), a heart attack or stroke
 - Yellowing of the skin or whites of the eyes (jaundice), or other liver problems
 - Migraine-type headaches that occur for the first time or more frequently (affects less than 1 in 10 users)
 - An increase in blood pressure
 - Breast or ovarian cancer, endometrial cancer or hyperplasia (long, heavy or irregular vaginal bleeding)
 - Convulsions (frequency unknown).

Inform the doctor if you notice any of the following side effects while using Evorel 50

Very common side effects – effects that occur in more than 1 in 10 users

- Irritation, itchiness and rash on the skin where the patch is applied.

Common side effects – effects that occur in 1-10 out of 100 users

- Red, puffy skin in the area where the patch is applied
- Breast pain
- Rash or feeling itchy
- Feeling dizzy
- Feeling depressed
- Headache
- Nausea or stomach pain
- Diarrhea
- Pain, including joint pain
- Breakthrough bleeding, spotting or periods
- Weight gain.

Uncommon side effects – effects that occur in 1-10 out of 1000 users

- Vaginal thrush
- Wind
- Rapid heartbeat (palpitations)
- Sensation of fullness in the breasts
- Painful period
- Swelling of the hands and feet (peripheral edema)
- Water retention or build-up of fluid under the skin (edema)
- Muscle pain
- Allergic reactions (hypersensitivity).

Rare side effects – effects that occur in 1-10 out of 10,000 users

- Bloated feeling
- Gallstones.

The following side effects have been reported with hormone replacement preparations other than Evorel 50

Common side effects – effects that occur in 1-10 out of 100 users

- Weight decrease
- Nausea.

Uncommon side effects – effects that occur in 1-10 out of 1000 users