

Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Evorel 50

Transdermal patch

Active ingredient and its quantity in a dosage unit:

estradiol (as hemihydrate) 3.2 mg

The transdermal patch delivers 50 mcg estradiol per day.

Inactive ingredients and allergens in the medicine - see section 6 "Additional information".

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your 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 to yours.

1. What is this medicine intended for?

To treat symptoms related to oestrogen deficiency in women after menopause or after surgical removal of the ovaries. The symptoms include hot flushes, insomnia, changes in the urogenital system, mood changes and bone loss, which may lead to osteoporosis.

In women who have not undergone hysterectomy, oestrogen therapy must be supplemented with sequential gestagen therapy.

Therapeutic group: estradiol

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to estradiol or to any of the other ingredients in this medicine (as listed in section 6 "Additional information")
- You have, have previously had or are suspected of having **breast cancer**
- You have or are suspected of having **a cancerous tumour which is worsened by oestrogens** (such as endometrial cancer)
- You have untreated **thickening of the lining of the womb** (endometrial hyperplasia)
- You have **unexplained vaginal bleeding**
- You have or have previously had **blood clots in the veins** (thrombosis), such as in the legs (deep venous thrombosis) or lungs (pulmonary embolism)
- You have a **blood clotting disorder** (such as protein C, protein S or antithrombin deficiency)
- You have or have previously had a liver disease and your liver function tests have not yet returned to normal
- You have or have recently had a disease caused by blood clots in the arteries, such as **angina pectoris, heart attack or stroke**
- You have a rare inherited blood problem called porphyria

Do not use the medicine if any of the above conditions applies to you. If you are not sure, consult your doctor or pharmacist before using Evorel 50.

If any of the above conditions appears for the first time during treatment with Evorel 50, stop using the medicine at once and consult your doctor immediately.

Special warnings about using this medicine

Medical history and check-ups

The use of hormone replacement therapy (HRT) carries risks which need to be considered when deciding whether to start or to continue treatment.

The experience in treating women with premature menopause (due to ovarian failure or surgery) is limited. In such cases, the risks of using HRT may be different. You should consult your doctor.

Before you start (or restart) HRT, your doctor will ask you about your own and your family's medical history. Your doctor may decide to perform a physical examination, which may include examination of your breasts and/or internal examination, if necessary.

Once you have started treatment with Evorel 50, you should see your doctor for periodic check-ups (at least once a year). At these check-ups, discuss with your doctor the benefits and risks of continuing treatment with the medicine.

You should perform periodic breast exams, as recommended by your doctor.

Before starting treatment, tell your doctor if you have ever had any of the following conditions, as these may return or become worse during treatment with Evorel 50. If so, you may need periodic check-ups more often.

- fibroids inside your womb
- growth of womb lining outside the womb (endometriosis) or a history of excessive growth of womb lining (endometrial hyperplasia)
- increased risk of developing blood clots [see "Blood clots in the vein (thrombosis)" below]
- increased risk of oestrogen-related cancerous tumours (for example, a mother, sister or grandmother who has had breast cancer)
- hypertension
- diabetes
- gallstones
- migraine or severe headaches
- a disease of the immune system affecting many organs of the body (systemic lupus erythematosus, SLE)
- epilepsy
- asthma
- a disease affecting the eardrum and hearing (otosclerosis)
- a liver problem, such as a benign liver tumour
- a very high level of triglycerides (fats) in the blood
- fluid retention due to heart or kidney problems
- hereditary and acquired angioedema
- a benign breast tumour (mastopathy)

Please make sure that you:

- Perform periodic breast exams and cervical smear tests
- Regularly check your breasts for any changes such as dimpling of the skin, changes in the nipple, or any lumps you can see or feel

Stop the treatment with Evorel 50 and see a doctor immediately in the following situations:

- any of the conditions listed above in section 2 "Do not use this medicine if";
- yellowing of the skin or whites of the eyes (jaundice). These may be signs of a liver disease;
- swollen face, tongue and/or throat and/or difficulty swallowing or hives (rash), together with difficulties breathing, which are suggestive of angioedema;
- a significant rise in blood pressure (symptoms may be headache, tiredness, dizziness);
- migraine-like headaches which occur for the first time;
- you become pregnant;
- if you notice signs of a blood clot, such as:
 - painful swelling and redness of the legs
 - sudden chest pain
 - difficulty breathing

For more information, see "Blood clots in the vein (thrombosis)".

Evorel 50 is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Contact your doctor for advice.

In addition to benefits, use of HRT is also associated with risks. Consider the following when deciding to take or continue HRT treatment.

Effect of HRT on heart and circulation

Heart disease (heart attack)

There is no evidence that HRT will prevent a heart attack.

Women over the age of 60 taking HRT containing oestrogen and progestogen are slightly more likely to develop heart diseases than women not treated with these products.

For women who have had hysterectomy and are taking oestrogen-only therapy, there is no increased risk of developing a heart disease.

Stroke

The risk of suffering a stroke is about 1.5 times higher in women taking HRT compared to women not taking HRT. The number of additional stroke cases due to the use of HRT increases with age.

Comparison

Looking at women in their 50s over a 5-year period, on average:

- 8 in 1000 women not taking HRT are expected to have a stroke
- 11 in 1000 women taking HRT are expected to have a stroke (3 additional cases).

If you have unexplained **migraine-type headaches**

- **See a doctor as soon as possible**
- **Do not use the HRT anymore** until your doctor confirms that you can.

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

Blood clots in the vein (thrombosis)

The risk of **blood clots in the veins** is 1.3 to 3 times higher in women taking HRT compared

to women not taking HRT, especially during the first year of using it.

These blood clots can be serious. If a blood clot travels to the lungs, it may cause chest pain, breathlessness, fainting or even death.

You are more likely to develop a blood clot in the vein as you get older and if any of the following applies to you. Inform your doctor if any of these conditions apply to you:

- you are seriously overweight (BMI >30 kg/m²)
- you have cancer
- any of your close relatives has ever had a blood clot in the leg, lung or another organ
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clot formation
- you are immobile for a long period because of major surgery, injury or illness (see "Operations or tests" below)
- you have systemic lupus erythematosus (SLE)

For signs of a blood clot, see above "Stop the treatment with Evorel 50 and see a doctor immediately in the following situations".

Comparison

Looking at women in their 50s over a 5-year period, on average:

- 4-7 in 1000 women who are not taking HRT are expected to have a blood clot
- 9-12 in 1000 women who are taking oestrogen-progestogen HRT are expected to have a blood clot (5 additional cases).

For women in their 50s who have had hysterectomy and are taking oestrogen-only HRT, 5 - 8 cases of blood clot formation in 1000 users are expected to occur (1 additional case).

HRT and cancer

Breast cancer

Evidence shows that taking oestrogen-progestogen or oestrogen-only HRT increases the risk of breast cancer. The additional risk depends on how long you have been taking HRT. The additional risk becomes clear within 3 years of use. After stopping HRT, the additional risk decreases with time, but the risk may persist for 10 years or more if you have taken HRT for more than 5 years.

Comparison

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

Regularly check your breasts. See your doctor as soon as possible if you notice any changes such as:

- Dimpling of the skin
- Changes in the nipple
- Any lumps you can see or feel

Additionally, you are advised to join mammography screening programs. It is important that you inform the healthcare professional who is performing the x-ray that you take HRT, as these medications may increase the density of the breast tissue, which may affect the outcome of the mammogram. When the density of the breast tissue is increased, the examination may not detect all the breast lumps.

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

Taking oestrogen-only HRT increases the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer).

Taking progestogen in addition to oestrogen for at least 12 days of each 28-day cycle protects you from this additional risk. So, your doctor will prescribe progestogen separately if you have not undergone hysterectomy. If you have undergone hysterectomy, discuss with your doctor whether you can safely use this medicine without progestogen.

In women who have not undergone hysterectomy and who are not using HRT, on average, 5 in 1000 will be diagnosed with endometrial cancer between the ages of 50 - 65.

In women aged 50 - 65 who have not undergone hysterectomy and who take oestrogen-only HRT, between 10 - 60 in 1000 will be diagnosed with endometrial cancer (i.e. between 5 and 55 additional cases), depending on the dose and treatment duration.

Ovarian cancer

Ovarian cancer is rare, much rarer than breast cancer.

The use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of ovarian cancer.

The risk of ovarian cancer varies with age. For example, in women aged 50 - 54 who are not taking HRT, 2 in 2000 women will be diagnosed with ovarian cancer over a 5-year period. In women who have been taking HRT for 5 years, 3 in 2000 women will be diagnosed with ovarian cancer (i.e. 1 additional case).

Other conditions

If you have **brown patches on your face or body (chloasma)** or have a history of them, you may need to keep out of the sun or away from sunbeds (these patches may not completely disappear again).

Dementia

Evorel 50 and medicines like it will not stop memory loss (dementia). Women who start using medicines like Evorel 50 after the age of 65 may have a small increase in the risk of dementia.

Smoking

Do not use the medicine without consulting your doctor if you are a smoker. It is recommended to quit smoking while using Evorel 50. If you cannot quit smoking and you are above the age of 35 years, consult your doctor. Smoking is a risk factor for venous thromboembolism (VTE).

Children and adolescents

The medicine is not intended for use in children.

Operations or tests

Tell your doctor if you are going to have surgery. You may need to stop taking HRT about 4 to 6 weeks before the operation to reduce the risk of a blood clot. Your doctor will tell you when you can start taking HRT again.

If you visit a hospital or your family doctor for a blood or urine test, tell them that you are taking Evorel 50. This is because Evorel 50 may affect the test results.

Drug interactions

If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist.

Some medicines may interfere with the effect of Evorel 50. This might lead to irregular bleeding.

Particularly if you are taking:

- Medicines for **epilepsy** (such as phenobarbital, phenytoin or carbamazepine).
- Medicines for **tuberculosis** (such as rifampicin, rifabutin)
- Medicines for **HIV infection** (such as nevirapine, efavirenz, ritonavir and nelfinavir)
- Herbal remedies containing **St John's Wort** (*Hypericum perforatum*);
- Medicines for Hepatitis C virus (HCV) (such as combination regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir, as well as a regimen with glecaprevir/pibrentasvir) may cause an increase in liver function blood test results (increase in ALT enzyme) in women using combined hormonal contraceptives containing ethinylestradiol. Evorel 50 contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Evorel 50 with this HCV combination regimen.

Pregnancy and breastfeeding

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

If you are pregnant, contact your doctor straight away and remove the patch.

Do not use this medicine if you are breastfeeding.

Evorel 50 is intended for use in postmenopausal women. If you become pregnant, stop using Evorel 50 and contact your doctor.

Driving and using machines

There is no information about whether Evorel 50 affects your ability to drive or use machines. Please check how this medicine affects you before driving or using heavy tools or machines.

3. How to use the medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dosage or about how to take this medicine. Only your doctor will determine your dosage and how you should take this medicine. The recommended dosage is usually:

The patches need to be changed twice a week. Start using a new pack of Evorel 50 as soon as you finish the previous pack, so there is no break between packs.

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

When to start treatment with Evorel 50**You may start treatment 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 previous HRT that did not cause you menstrual bleeding.

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

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

Apply an Evorel 50 patch at the end of a treatment cycle or one week after you finish treatment with another HRT medicine if:

- You are changing from an HRT medicine that caused you menstrual bleeding.

If you are taking another HRT:

- The day you start treatment with Evorel 50 depends on the type of the other HRT.
- Contact your doctor if you are not sure which type of HRT you are using.

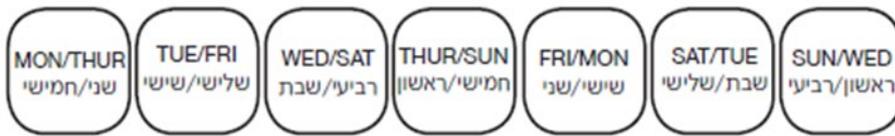
Changing Evorel 50 patches

- You must change the patches twice a week to give your body a steady supply of hormones. There are enough hormones in each patch to last for several days.
- Change your patch on the same days twice a week. This means that one patch will be on for three days, and the next patch for four days.
- For example, if you apply your first patch on Monday, change it on Thursday and again on the following Monday. You can determine the two changing days by the following table:

If you apply the 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 changing days, mark them on the pack. They are written

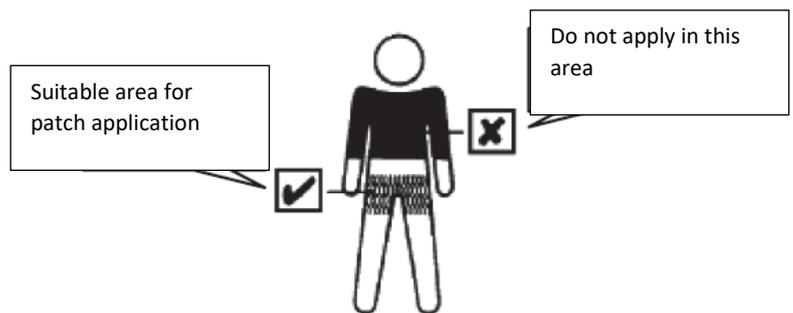
on the pack as follows:



Where to apply the patch

Stick the patch onto a hairless area of skin below the waist. Most women prefer to apply the patch on the thigh or bottom.

- Do not apply on or near the breasts.
- Do not apply on top of skin cuts, spots or anywhere the skin is irritated.
- Do not use cream, moisturiser or talc before applying the patch.
- Do not apply the patch on the same area of skin twice in a row.
- The patch can be applied under loose areas of clothing.
- Do not apply the patch under elastic bands or rubber.
- Apply the patch to clean, dry, cool skin immediately after taking it out of the protective pouch.

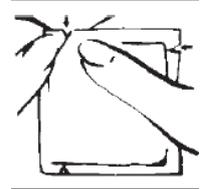


Applying a patch

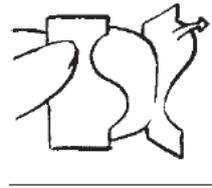
Do not use a patch if its protective pouch is already open.

Step 1: Open and peel

- Using the notches as a guide, tear along two edges of the pouch and remove the patch.



- Hold the patch with the patch cover (aluminium like foil) facing you, bend the patch and remove part of the aluminium foil covering the patch. Avoid touching the sticky side of the patch - it may not stick properly



Step 2: Apply and press

- Apply the exposed part of the patch to your skin.
- Peel the second half of the aluminium like foil and attach the second half of the patch to the skin.



- Attach the patch to the skin with the palm of your hand to make sure it is firmly attached.



Removing a patch

- Peel the edges of the patch from the skin and pull it off gently.
- Fold the patch in half, so that the sticky side sticks to itself.
- Discard the patch in the household rubbish, out of the reach of children and pets.
- Do not flush used patches down the toilet.



After removing the patch, some glue may remain on your skin. It will disappear with time. You can use baby oil to remove glue residues.

If a patch falls off

Replace the patch that fell off with a new patch, but keep your regular patch changing days. If you have just had a bath or shower, 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 and keep your regular patch changing days. You may experience spotting or menstruation like bleeding during this time.

If you use more Evorel 50 than you should

It is unlikely that you will reach too much of the hormones contained in Evorel 50. The most

common symptoms of high oestrogen levels in the body are:

- Tender or painful breasts
- Nausea or vomiting
- Unexpected vaginal bleeding
- Abdominal pain or bloating

These symptoms resulting from oestrogen excess are reversible upon patch removal. Consult your doctor or pharmacist before using additional patches. Your doctor may decide to change the treatment.

Contraception while using Evorel 50

The levels of hormone in the product are too low to act as a contraceptive. Use non-hormonal contraceptive methods (such as a condom, diaphragm or coil) until your periods have completely stopped.

Everyday activities

- You can have a bath or shower as normal. Do not scrub the skin around the patch too hard as this can loosen the patch edges.
- You can go swimming. The patch will not be affected by this activity.
- You can engage in sports. Do not apply the patch under tight clothing or elastic bands.
- You can sunbathe. However, ensure that the patch is covered and not exposed to direct sunlight.

Adhere to the treatment as recommended by your doctor.

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

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects

Like with any medicine, using Evorel 50 may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Some side effects may be caused by progestogen that is being taken at the same time.

The following diseases are reported more often in women taking HRT compared to women not taking HRT:

- breast cancer
- abnormal growth or cancer of the lining of the womb (endometrial hyperplasia or cancer)
- ovarian cancer
- blood clots in the veins of the legs or lungs (venous thromboembolism)
- heart disease
- stroke
- possible memory loss if HRT is started over the age of 65

For more information about these side effects, see section 2 in the leaflet.

Remove the patch and tell your doctor straight away if you notice or suspect any of the following. 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 occurs only 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 occurring 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 (prolonged, heavy or abnormal vaginal bleeding)
- Seizures (unknown frequency).

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

Very common side effects - affect more than 1 in 10 users

- Irritated, itchy skin and rash where the patch is applied.

Common side effects - affect 1-10 in 100 users

- Red, puffy skin where the patch is applied
- Breast pain
- Rash or feeling itchy
- Feeling dizzy
- Feeling depressed
- Headache
- Nausea or abdominal pains
- Diarrhoea
- Pain, including joint pain
- Breakthrough bleeding, spotting or period
- Weight gain.

Uncommon side effects - affect 1-10 in 1000 users

- Vaginal thrush
- Wind
- Accelerated heartbeats (palpitations)
- Sensation of breast fullness
- Painful periods
- Swelling of hands and feet (peripheral oedema)
- Water retention or build-up of fluid under the skin (oedema)
- Muscle pain
- Allergic reactions (hypersensitivity).

Rare side effects - affect 1-10 in 10,000 users

- Bloating feeling
- Gallstones.

The following side effects have been reported with other HRTs

Common side effects - affect 1-10 in 100 users

- Weight decrease
- Nausea.

Uncommon side effects - affect 1-10 in 1000 users

- Problems with sight
- Indigestion
- Painful reddish skin nodules (erythema nodosum)
- Tender breasts.

Rare side effects - affect 1-10 in 10,000 users

- Feeling anxious
- Increase or loss of sex drive
- Vomiting
- Sensation of discomfort while using contact lenses
- Excessive hair growth
- Acne
- Muscle cramps
- Discharge from the vagina, premenstrual syndrome (PMS)
- Feeling tired.

The following side effects have been reported in association with oestrogen/progestogen treatment

- Gallbladder disease
- Brown patches on the face or body, discoloration of the skin, especially of the face or neck, called “pregnancy patches” (chloasma)
- Rash with target-shaped reddening or sores (erythema multiforme)
- Appearance of painful reddish skin nodules (erythema nodosum)
- Bruising on the legs
- Loss of memory (dementia), see section 2.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link ‘Reporting Side Effects of Drug Treatment’ on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: <https://sideeffects.health.gov.il>

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.
- Do not store above 25°C.
- Store in the original package.
- Do not use a patch if the protective pouch is already open.

6. Additional information

- **In addition to the active ingredient, this medicine also contains** Duro-Tak (acrylate vinylacetate copolymer), hostaphan MN19 (polyethyleneterephthalate foil) and guar gum (meyprogat)

- **What the medicine looks like and contents of the pack**
Evorel 50 comes in a memory pack containing 8 patches. The patch is marked with CE50 and has a surface area of 16 cm².
The patches are square with rounded edges. The patches are clear with a sticky side that is applied to the skin. Each patch comes in a protective sealed pouch.
- **Registration holder's name and address:**
Truemed Ltd., Netanya 4250499, Israel
- **Manufacturer's name and address:**
Theramex Ireland Ltd., Dublin, Ireland
- This leaflet was revised in December 2022 according to MOH guidelines.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
103-09-28671

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