

EVOREL GEL

PACKAGE LEAFLET: INFORMATION FOR THE USER

Evorel Gel 500 micrograms/actuation transdermal gel

Estradiol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist, this includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

1. What Evorel Gel is and what is used for

Evorel Gel is a Hormone Replacement Therapy (HRT). It contains the female hormone oestrogen. Evorel Gel is used for:

Relief of symptoms occurring after menopause

During the menopause, the amount of the oestrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ("hot flushes"). Evorel Gel alleviates these symptoms after menopause. You will only be prescribed Evorel Gel if your symptoms seriously hinder your daily life.

The experience in treating women older than 65 years is limited.

2. What you need to know before you use Evorel Gel

Medical history and regular check-ups:

The use of HRT carries risks which need to be considered when deciding whether to start taking it, or whether to carry on taking it.

The experience in treating women with a premature menopause (due to ovarian failure or surgery) is limited. If you have a premature menopause the risks of using HRT may be different. Please talk to your doctor.

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

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

Go for regular breast screening, as recommended by your doctor.

Do not use Evorel Gel:

if any of the following applies to you. If you are not sure about any of the points below, talk to your doctor before taking Evorel Gel,

Do not use Evorel Gel:

- if you have or have ever had **breast cancer**, or if you are suspected of having it;
- if you have **cancer which is sensitive to oestrogen**, such as cancer of the womb lining (endometrium), or if you are suspected of having it;
- if you have any **unexplained vaginal bleeding**;
- if you have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated;
- if you have or have ever had a **blood clot in a vein** (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism);
- if you have a **blood clotting disorder** (e.g. Protein C, Protein S, or antithrombin deficiency);
- if you have or recently have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke or angina**;
- if you have or have ever had a **liver disease** and your liver function tests have not returned to normal;
- if you have a rare blood problem called “porphyria” which is passed down in families (inherited);
- if you are **allergic to estradiol** or any of the other ingredients of this medicine (listed in section 6).

If any of the above conditions appear for the first time while taking Evorel Gel, stop taking it at once and consult your doctor immediately.

When to take special care with Evorel Gel:

Tell your doctor if you have ever had any of the following problems, before you start the treatment, as these may return or become worse during treatment with Evorel Gel. If so, you should see your doctor more often for check-ups:

- fibroids inside your womb;
- growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia);
- increased risk of developing blood clots (see “Blood clots in a vein (thrombosis)”);
- increased risk of getting an oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer);
- high blood pressure;
- a liver disorder, such as a benign liver tumour;
- diabetes;
- gallstones;
- migraine or severe headaches;
- a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE);
- epilepsy;
- asthma;
- a disease affecting the eardrum and hearing (otosclerosis);
- a very high level of fat in your blood (triglycerides);
- fluid retention due to cardiac or kidney problems;
- hereditary and acquired angioedema.

Stop using Evorel Gel and see a doctor immediately

If you notice any of the following when taking HRT:

- any of the conditions mentioned in the 'DO NOT use Evorel Gel' section;
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease;
- swollen face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing which are suggestive of an angioedema;
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness);
- migraine-like headaches which happen for the first time;
- if you become pregnant;
- if you notice signs of a blood clot, such as:
 - painful swelling and redness of the legs;
 - sudden chest pain;
 - difficulty in breathing.

For more information, see 'Blood clots in a vein (thrombosis)'.

Note: Evorel Gel 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. Speak to your doctor for advice.

HRT and cancer

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

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

Taking a progestogen in addition to the oestrogen for at least 12 days of each 28 day cycle protects you from this extra risk. So your doctor may prescribe a progestogen separately if you still have your womb. If you have had your womb removed (a hysterectomy), your doctor will discuss with you whether you can safely take this product without a progestogen.

In women who still have a womb and who are not taking HRT, on average, 5 in 1000 will be diagnosed with endometrial cancer between the ages of 50 and 65.

For women aged 50 to 65 who still have a womb and who take oestrogen-only HRT, between 10 and 60 women in 1000 will be diagnosed with endometrial cancer (i.e. between 5 and 55 extra cases), depending on the dose and for how long it is taken.

Unexpected bleeding

If your doctor has prescribed you progestogen tablets in addition to Evorel Gel, you will usually have a bleed once a month (so-called withdrawal bleed). But, if you have unexpected bleeding or drops of blood (spotting) besides your monthly bleeding, which:

- carries on for more than the first 6 months;
- starts after you have been using Evorel Gel more than 6 months;
- carries on after you have stopped using Evorel Gel;

see your doctor as soon as possible.

Breast cancer:

Evidence shows that taking combined oestrogen-progestogen and/or oestrogen-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

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time, but the risk may persist for 10 years or more if you have used HRT for more than 5 years.

Compare

Women aged 50 to 54 who are not taking HRT, on average, 13 to 17 in 1,000 will be diagnosed with breast cancer over a 5-year period.

For women aged 50 who start taking oestrogen-only HRT for 5 years, there will be 16-17 cases in 1000 users (i.e. an extra 0 to 3 cases).

For women aged 50 who start taking oestrogen-progestogen HRT for 5 years, there will be 21 cases in 1,000 users. (i.e. an extra 4 to 8 cases).

Women aged 50 to 59 who are not taking HRT, on average, 27 in 1000 will be diagnosed with breast cancer over a 10-year period.

For women aged 50 who start taking oestrogen-only HRT for 10 years, there will be 34 cases in 1000 users (i.e. an extra 7 cases)

For women aged 50 who start taking oestrogen-progestogen HRT for 10 years, there will be 48 cases in 1000 users (i.e. an extra 21 cases).

• **Regularly check your breasts. See your doctor 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 when offered to you. For mammogram screening, it is important that you inform the nurse/healthcare professional who is actually taking the x-ray that you use HRT, as this medication may increase the density of your breasts which may affect the outcome of the mammogram. Where the density of the breast is increased, mammography may not detect all lumps.

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 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2000 users. (i.e. about 1 extra case).

Effects of HRT on heart and circulation

Blood clots in a vein (thrombosis)

The risk of **blood clots in the veins** is about 1.3 to 3 times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

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

- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, If you need to have surgery);
- you are seriously overweight (BMI >30 kg/m²);
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots;
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ;

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- you have systemic lupus erythematosus (SLE);
- you have cancer.

For signs of a blood clot, see “Stop using Evorel Gel and see a doctor immediately”.

Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1,000 would be expected to get a blood clot in a vein.

For women in their 50s who have been taking oestrogen-progestogen HRT for over 5 years, there will be 9 to 12 cases in 1000 users (i.e. an extra 5 cases).

For women in their 50s who have had their womb removed and have been taking oestrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1000 users (i.e. 1 extra case).

Heart disease (heart attack)

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

Women over the age of 60 years who use oestrogen-progestogen HRT are slightly more likely to develop heart disease than those not taking any HRT.

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

Stroke

The risk of having a stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Compare

Looking at women in their 50s who are not taking HRT, on average, 8 in 1000 would be expected to have a stroke over a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1000 users, over 5 years (i.e. an extra 3 cases).

Other conditions

HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Possible transfer of estradiol:

During close skin contact estradiol may be transferred to another person unless you cover the treated area.

The following precautions are therefore recommended:

- wash your hands with soap and water after applying the gel,
- cover the application area with clothing once the gel has dried,
- take a shower before intimate contact.

If you believe estradiol has been transferred to another person (man or child), wash the area of skin which may have been affected with soap and water.

Children

Estradiol gel can be accidentally transferred from the skin to other people. Do not allow others, especially children, to come into contact with the exposed area of your skin and cover the area, if needed, after the gel has dried. If a child comes into contact with the area of the skin where estradiol was applied on, wash the child's skin with soap and water as soon as possible. Due to the estradiol transfer, young children may show signs of puberty that are not expected (for example breast budding). In most cases the symptoms will disappear when children are no longer exposed to estradiol gel.

Contact your healthcare provider if you see any signs and symptoms (breast development or other sexual changes) in a child that may be exposed accidentally to estradiol gel.

Other medicines and Evorel Gel

Some medicines may interfere with the effect of Evorel Gel. This might lead to irregular bleeding. This applies to the following medicines:

- Medicines for **epilepsy** (such as phenobarbital, phenytoin, carbamazepim),
- Medicines for **tuberculosis** (such as rifampicin, rifabutin),
- Medicine for **HIV infection** (such as nevirapine, efavirenz, ritonavir and nelfinavir),
- Herbal remedies containing **St. John's Wort** (*Hypericum perforatum*).

HRT can affect the way some other medicines work:

- A medicine for epilepsy (lamotrigine), as this could increase frequency of seizures.
- Medicines for Hepatitis C virus (HCV) such as combination regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; glecaprevir/pibrentavir or sofosbuvir/velpatasvir/voxilaprevir may cause increase in liver function blood test results (increase in ALT liver enzyme) in women using CHC's containing ethinylestradiol. Evorel Gel contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Evorel Gel with this HCV combination regimen.

Please tell your doctor or pharmacist if you are using, have recently used or might use any other medicines including medicines obtained without a prescription, herbal medicines or other natural products. Your doctor will advise you.

Laboratory tests

If you need a blood test, tell your doctor or the laboratory staff that you are using Evorel Gel, because this medicine can affect the results of some tests.

Pregnancy and breast-feeding

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

Driving and using machines

No particular effect is expected.

Evorel Gel contains propylene glycol

Evorel Gel contains propylene glycol which may cause skin irritation.

3. How to use Evorel Gel

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

Using this medicine

- If you have never used any other HRT medicines or you are switching to Evorel Gel from a period-free HRT product, you can start using Evorel Gel on any convenient day.
- If you are currently using another type of HRT where you have a period, finish your current medicine pack before you start using Evorel Gel.
- Do not ask anyone else to apply the gel. Only you should apply your medicine.
- Do not allow other people to touch the area of the skin where the gel was applied and cover with clothing, if needed, after the gel has dried.
- Do not wash the skin or apply other skin care products for at least one hour after application.

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- If you have noticed that the effect of Evorel Gel is too strong or too weak, inform your doctor. Do not use more than the prescribed dose.
- Bleeding similar to your period may occur during the period of interruption of treatment. This bleeding is normal and limited in nature.
- For women with an intact uterus the addition of a progestational hormone for at least 12 days per cycle is mandatory to prevent the risk of overdevelopment of the lining of the uterus (estrogen-induced endometrial hyperplasia).

Your health care provider will prescribe Evorel Gel in accordance with your needs. He/she may modify the dosage and duration of the treatment depending on your response to the treatment. Your doctor will aim to prescribe the lowest dose to treat your symptom for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

Route of administration:

This medicine should be applied on the skin.

Preparing the pump

Before using a **new pump for the first time**, you need to prepare it for use as follows:

- Remove the cap
- Press the pump several times until the gel comes out to prime the pump
- The first dose may not be exact, and you should discard it.
- The pump is now ready to use.
- The pump may need to be reprimed after first use.

How much to use and when to use

- The gel should be applied preferably after washing in the morning or evening, once a day.
- Try to use the gel approximately the same time each day.
- Your doctor will prescribe the lowest dose for the shortest time to treat your symptoms.
- The individual dose can range from 0.5 to 3 g of gel per day
- The usual dose is 1.5 g of gel per day, (3 presses of the metering pump) to be taken for 24 to 28 days per month followed by 2 to 7 days without treatment. Each pump delivers a dose of 0.5 g of gel.
- The gel should be applied on a clean, dry, and intact skin (on the abdomen, thighs, arms or shoulders).
- Your doctor may also prescribe Evorel Gel to be used continuously without interruption.
- On average, the 50 g bottle is sufficient for one month's treatment.

How to apply Evorel Gel:

- Remove the cap.
- Hold the bottle with one hand and place the other hand under the nozzle to catch the gel and press the metering pump to obtain the required dose.
- Between each press, allow the nozzle to return to its initial position.
- The gel should be applied to the abdomen, thighs, arms or shoulders, over an area equivalent to twice the size of a hand.
- **The gel must not be applied to the breasts or mucous membranes (lining of the mouth, nose, ears or genital organs).**
- You should avoid contact with your eyes.
- Massage is not required but it is recommended to leave the gel to dry for 2 minutes before getting dressed. The gel does not stain.
- Wash hands with soap and water after applying the gel.

If you believe Evorel Gel has been transferred to another person (man or child):

Wash the area of skin which may have been affected immediately with soap and water.

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Duration of treatment:

Follow your doctor's prescription. The doctor will decide on the duration of treatment, they may however need to modify it.

If you wish to stop treatment before this time you should discuss this with your doctor.

If you use more Evorel Gel than you should:

Overdose may cause nausea, vomiting, and vaginal bleeding. No specific treatment is required.

If the signs persist, ask your doctor for advice.

If you forget to use Evorel Gel:

- Do not take a double dose to make up for a forgotten dose.
- If you have forgotten to apply the gel on the scheduled day, apply it as soon as possible and resume treatment with the prescribed dosage.
- If you have not applied the gel for several days, irregular bleeding may occur. If you are in doubt, consult your doctor.

If you stop using Evorel Gel:

Upon cessation of treatment, signs of menopause-related estrogen deficiency may reappear.

If you have any further questions, ask your doctor or your pharmacist.

If you need to have surgery

If you are going to have surgery, tell the surgeon that you are using Evorel Gel. You may need to stop using Evorel Gel about 4 to 6 weeks before the operation to reduce the risk of a blood clot (see section 2, Blood clots in a vein). Ask your doctor when you can start using Evorel Gel again.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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

Common (may occur in 1 to 10 patients from 100):

- abnormal and irregular uterine or vaginal bleeding (dysmenorrhea, breakthrough bleeding or spotting),
- headache,
- abdominal pain,
- nausea,
- rash,
- itching (pruritus),
- changes in weight (increase or decrease),

Uncommon (may occur in 1 to 10 patients from 1000):

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- allergy (hypersensitivity reaction),
- depressed mood and mood disturbances,
- dizziness,
- visual disturbances,
- palpitations,
- stomach pain (dyspepsia),
- skin inflammation that results in reddish, painful, tender lumps (erythema nodosum),
- skin pigmentation disorder (chloasma/melasma),
- urticaria,
- swelling (oedema),
- breast pain,
- breast tenderness.

Rare (may occur in 1 to 10 patients from 10 000):

- excess hair on the face and body (hirsutism),
- breast enlargement,
- bloating,
- intolerance to contact lenses,
- migraine,
- anxiety,
- libido modification (increase or decrease)
- vomiting,
- acne,
- muscle cramps,
- fatigue,
- premenstrual-like syndrome (i.e. fatigue, abdominal pain, headache, breast tenderness, irritability),
- vaginal discharge (leucorrhoea).

The following side effects have been reported with other HRTs:

- gall bladder disease,
- various skin disorders,
- discoloration of the skin especially of the face or neck known as “pregnancy patches” (chloasma),
- painful reddish skin nodules (erythema nodosum),
- rash with target-shaped reddening or sores (erythema multiforme).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly to ***the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.*** By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Evorel Gel

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Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and on the bottle. The expiry date refers to the last day of that month.

Do not refrigerate or freeze.

Do not use this medicine if you notice visible signs of deterioration.

Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Evorel Gel contains

The active substance is: Estradiol (1 mg for 1 g of gel). Each actuation of the pump delivers 0.5 g of gel corresponding to 0.5 mg of estradiol.

The other ingredients are: 96 percent ethanol, purified water, propylene glycol, diethylene glycol monoethylether (TRANSCUTOL[®]), carbomer (CARBOPOL[®] 1382), trolamine, edetate disodium.

What Evorel Gel looks like and contents of the pack

- Gel for transdermal use in 50 g bottle with metered-dose pump. Box of one or three bottles
- This medicine is a clear, translucent, colourless-to-slight yellowish and odourless gel.
- Evorel Gel bottle delivers 84 metered doses.
- Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Theramex HQ UK Limited
5th Floor, 50 Broadway
London, SW1H 0BL
United Kingdom

Manufacturer

Theramex Poland Sp. z o. o.
Amsterdam Building
ul. Poleczki 35
02-822 Warszawa
Poland

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