

PACKAGE LEAFLET

Package leaflet: Information for the user
Evorel® 50 micrograms per 24 hours Transdermal Patch
Estradiol hemihydrate

Evorel is a registered trademark

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 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

The name of your medicine is Evorel 50 micrograms per 24 hours Transdermal Patch. It is called Evorel in this leaflet. Evorel is a Hormone Replacement Therapy (HRT). It contains the female hormone oestrogen. Evorel is used in postmenopausal women with at least 18 months since their last natural period.

Evorel comes in a 'memory pack'. This can be used to help you remember when to change your patches. Each pack contains eight patches.

The hormone is spread evenly in each patch. It passes slowly into your body through the skin.

Evorel 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 alleviates these symptoms after menopause. You will only be prescribed Evorel if your symptoms seriously hinder your daily life.

• **Prevention of osteoporosis**

After the menopause some women may develop fragile bones (osteoporosis). You should discuss all available options with your doctor.

If you are at an increased risk of fractures due to osteoporosis and other medicines are not suitable for you, you can use Evorel to prevent osteoporosis after menopause.

How Evorel works

Evorel patches replace the oestrogen that is normally released by the ovaries. However, in women who still have a womb, taking an oestrogen hormone regularly may cause the lining of your womb to build up and get thicker.

- This means it is necessary to add a progestogen hormone to the oestrogen
- This helps shed the lining of the womb and stop any problems happening

Note: Evorel 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.

2. What you need to know before you use Evorel

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) 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 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 risks of continuing with Evorel.

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

Do not use Evorel

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.

Do not take Evorel if:

- You have or have ever had **breast cancer**, or if you are suspected of having it;
- You have **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it;
- You have any **unexplained vaginal bleeding**;
- You have **excessive thickening of the lining of the womb** (endometrial hyperplasia) that is not been treated;
- You have or have ever had **blood clot in a vein** (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism);
- You have a **blood clotting disorder** (such as protein C, protein S or antithrombin deficiency);
- You have or recently have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke** or **angina**;

- You have or have ever had a **liver disease** and your liver function tests have not returned to normal;
- You have a rare blood problem called “porphyria” which is passed down in families (inherited);
- You are **allergic** (hypersensitive) to **estradiol hemihydrate** or any of the other ingredients of Evorel (listed in section 6 Further information);

Stop using Evorel at once if any of the above appears for the first time and see your doctor immediately.

When to take special care with Evorel

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. If so, you should see your doctor more often for check-ups:

- fibroids inside your womb;
- growth of the 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 and see a doctor immediately

If you notice any of the following when using HRT:

- any of the conditions mentioned in the ‘DO NOT use Evorel’ 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)"

If you have had a premature menopause the risk of using HRT may be different. Talk to your doctor about the risks.

Safety of HRT

As well as benefits, HRT has some risks. Consider the following when deciding to have or continue HRT.

HRT and Cancer

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

HRT is **not recommended** for women who have ever had cancer of the lining of the womb.

Using 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 will prescribe a progestogen separately if you still have your womb. If you have had your womb removed (a hysterectomy), discuss with your doctor whether you can safely take this product without a progestogen.

How likely is endometrial cancer?

Looking at women aged 50 to 65 years, who still have a womb, on average, over the next 15 years:

- In women **not taking HRT - 5 in 1000** will get endometrial cancer
- In women **taking oestrogen-only HRT**, the number will be **2 to 12 times higher (an extra 5 to 55 cases)**, depending on the dose and how long you take it for

The addition of a progestogen to oestrogen-only HRT substantially reduces the risk of endometrial cancer.

Breast cancer

Evidence shows that taking combined oestrogen-progestogen 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 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?

Women aged 50 to 54 who are not taking HRT, on average 13 to 17 in 1000 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 1000 users (i.e. an extra 4-8 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).

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

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

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

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).

Effect 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 using 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;
- any of your close relatives has ever had blood clot in the leg, lung or another organ;
- you have systemic lupus erythematosus (SLE);
- you have cancer.

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

How likely is a blood clot?

Looking at women aged 50-59 years, on average, over 5 years:

- In women **not taking HRT** – **between 4 and 7 in 1000** would be expected to get a blood clot
- In women, who have had their womb removed, **taking oestrogen only HRT** – **between 5 and 8 in 1000** would be expected to get a blood clot (an **extra 1 case**)
- In women taking **oestrogen-progestogen HRT** – **between 9 and 12 in 1000** would be expected to get a blood clot (an **extra 5 cases**)

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.

If you get a **pain in your chest** that spreads to your arm and neck

- **See a doctor as soon as possible**
- **Do not have any more HRT** until your doctor says you can This pain may be a sign of heart disease.

Stroke

The risk of getting 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.

Looking at women aged 50-59 years, on average, over 5 years:

- In women **not taking HRT** - **8 in 1000** would be expected to have a stroke
- In women **taking HRT** - **11 in 1000** would be expected to have a stroke (an **extra 3 cases**)

If you get **migraine-type headaches** which you cannot explain

- **See a doctor as soon as possible**
- **Do not have any more HRT** until your doctor says you can These headaches may be an early warning sign of a stroke.

Dementia

- Evorel and medicines like it will not stop memory loss (dementia). Women who

start using medicines like Evorel after the age of 65 may have a small increase in the risk of dementia.

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)

Using other medicines

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

- Medicines to help you sleep (called barbiturates)
- A medicine for pain and inflammation called phenylbutazone
- A medicine for anxiety called meprobamate
- 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 increases in liver function blood test results (increase in ALT liver enzyme) in women using CHCs containing ethinylestradiol. Evorel contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Evorel with this HCV combination regimen. Your doctor will advise you.
- A medicine for high blood pressure in the blood vessels of the lungs called bosentan
- A medicine for epilepsy called lamotrigine

Using Evorel with lamotrigine could affect control of your epilepsy.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription, herbal medicines or other natural products.

Operations or tests

Tell your doctor if you are going to have surgery. You may need to stop using 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 using HRT again.

If you visit a hospital or your family doctor for a blood or urine test, tell them that you are using Evorel. This is because this medicine may affect the results of the tests.

Pregnancy and breast-feeding

Evorel is for use in postmenopausal women only.

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

Driving or using machines

There is no information about whether Evorel affects your ability to drive or use machines. See how this medicine affects you before you drive or use any tools or machines.

3. How to use Evorel

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

The highest dose you should have is 100 micrograms of estradiol in a day. This is the amount delivered by two Evorel 50 patches each day.

When to start using Evorel

Put an Evorel patch on at the end of a treatment cycle if:

- You are changing from an HRT medicine that gives you a withdrawal bleed

You may put an Evorel patch on at any time if:

- You have not used HRT before your menopause
- You are changing from HRT that does not give you a withdrawal bleed Talk to your doctor if you are not sure which type of HRT you are using.

Using the patches

The patches need to be changed twice a week.

Start a new pack of Evorel as soon as you finish one. Do not leave a break between packs.

Changing your patches

- You must 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 your patch on the same two days every week. This will mean that one patch is on for three days and the next patch for four days
- For example, if you apply your first patch on a Monday, change it 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:

Monday

→

Change on:

Thursday

&

Change again on:

Monday

Tuesday

→

Friday

&

Tuesday

Wednesday

→

Saturday

&

Wednesday

Thursday

→

Sunday

&

Thursday

Friday

→

Monday

&

Friday

Saturday

→

Tuesday

&

Saturday

Sunday

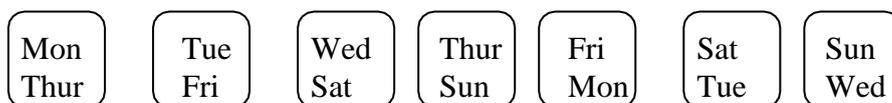
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Wednesday

&

Sunday

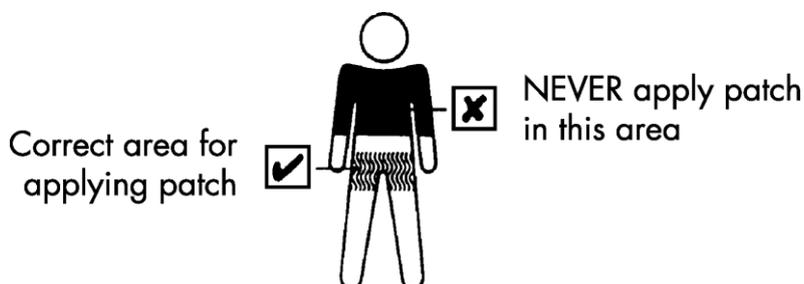
To help you remember your two "patch change" days, mark them here or on the pack. They are written on the pack like this:



Where to apply the patch

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

- Do not apply on or near the breasts
- Do not put it on top of 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
- It can be worn under loose areas of clothing. Do not wear a patch under elasticated areas or a tight waistband
- Apply the patch to clean, dry, cool skin as soon as you open the protective pouch

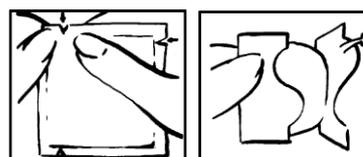


Putting a patch on

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

Step 1: Open and Peel

- Using the notches as a guide, tear along two edges of the pouch. Remove the patch
- With the protective backing facing you, bend and peel off half the backing. Don't touch the sticky side - it may not stick properly if you do



Step 2: Apply and Press

- Apply the open half of the patch to your skin
- Remove the remaining backing and press down the rest of the patch
- Press the patch with the palm of your hand to make sure it is firmly stuck



Removing a patch

- Peel an edge of the patch smoothly away from the skin
- Fold the patch in half, so that the sticky side sticks to itself



- Put it safely out of
- the reach of children and pets (see section 5)
- Do not flush used patches down the toilet

When you remove the patch some glue may remain on your skin. It will disappear with time, or you can use baby oil to remove it.

If a patch falls off

Apply a new patch but 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.

Talk to your doctor if you need more patches.

If you forget to change the patch

Change it as soon as you remember and then keep to your original 'patch change' days. You may get some bleeding and spotting like a period during this time.

If you use more Evorel than you should

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

- Tender or painful breasts
- Feeling sick (nausea) or being sick
- Unexpected vaginal bleeding
- Stomach pain or bloating

Removing the patch can reverse the effects of too much oestrogen. Talk to your doctor or pharmacist before using any more patches. Your doctor may decide to change the size of patch.

Contraception while using Evorel

The levels of hormone from the patches are too low to act as a contraceptive. Talk to your doctor for advice on contraception.

Everyday activities

- You can have a bath or shower as normal. Do not scrub too hard as this can loosen the edges of the patch
- You can go swimming. The patch will not be affected
- You can exercise and play sports. However, do not wear the patch under tight clothing or waist bands
- You can sunbathe. However, keep the patch covered, out of direct sunlight

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some side effects may be due to any progestogen that is being taken at the same time.

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
- probable memory loss if HRT is started over the age of 65 For more information about these side effects, see Section 2.

Take off 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 may cause difficulty in swallowing or breathing. This may be a sign of an allergic reaction. This only happens in a small number of people
- Blood clots (thrombosis), a heart attack or stroke
- Breast cancer or ovarian cancer
- Yellowing of the skin or whites of the eyes (jaundice), or other liver problems
- Migraine-type headaches for the first time or more frequent (affects less than 1 in 10 people)
- A large increase in blood pressure
- Endometrial cancer or hyperplasia (long, heavy or irregular vaginal bleeding)
- Convulsions or fits (frequency unknown)

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

Very common (affects more than 1 in 10 people)

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

Common (affects fewer than 1 in 10 people)

- Red puffy skin where the patch is applied
- Breast pain
- Rash or feeling itchy
- Feeling dizzy
- Feeling depressed
- Headache
- Diarrhoea
- Feeling sick or having stomach pains
- General pain and pain in the joints
- Break through bleeding, spotting or periods
- Weight gain

Uncommon (affects fewer than 1 in 100 people)

- Vaginal thrush
- Wind
- Being aware of your heart beat (palpitations)
- Fuller breasts
- Painful periods
- Swelling of hands and feet (peripheral oedema)
- Water retention, build-up of fluid under the skin (oedema)
- Muscle pain
- Allergic reaction (hypersensitivity)

Rare (affects fewer than 1 in 1,000 people)

- Bloating feeling
- Gallstones

The following side effects have been reported with other HRTs:

Common (affects fewer than 1 in 10 people)

- Weight decrease
- Feeling sick

Uncommon (affects fewer than 1 in 100 people)

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

Rare (affects fewer than 1 in 1,000 people)

- Feeling anxious
- Increase or loss in sex drive
- Being sick
- Contact lenses may feel uncomfortable
- Excess 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

- Gall bladder disease
- Brown patches on your face or body (chloasma)
- Painful reddish skin nodules (erythema nodosum)
- Rash with target -shaped reddening or sores (erythema multiforme)
- Bruising on the legs
- Loss of memory (Dementia) (see section 2)

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 via website: www.hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Evorel

Keep this medicine out of the sight and reach of children. Do not store above 25°C. Keep in the original pouch and carton.

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

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

Do not throw away any unused patches via wastewater or household waste. Ask your pharmacist how to throw away medicines you wanton longer use. This measures will help to protect the environment.

6. Contents of the pack and other information

What Evorel contains

Active substance

Each patch contains 3.2 mg estradiol hemihydrate and delivers 50 micrograms of estradiol a day.

Other ingredients

Evorel also contains Duro-Tak 387-2287 (this makes the patches sticky), guar gum and Hostaphan MN19 (backing film).

What Evorel looks like and contents of the pack

Each box of Evorel comes in a memory pack containing eight patches. Evorel 50 is marked CE50 and has a surface area of 16 sq cm.

The patches are square with rounded corners. They are clear with a sticky backing that can be stuck to the skin. Each patch comes in a protective sealed pouch.

Marketing authorisation holder:

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