

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS’ REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor’s prescription only

Evorel® Conti Transdermal Patch

Active ingredients and their quantity per dosage unit:
Each patch contains:

- estradiol hemihydrate 3.2 mg**
- norethisterone acetate 11.2 mg**

Release rate:
50 mcg estradiol/24 hours
170 mcg norethisterone acetate/24 hours

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

Read this 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?

Hormone replacement therapy (HRT) for the relief of menopausal symptoms.

Therapeutic group: a combination of estrogen and progestogen.

Menopause happens when the level of hormones produced by the ovaries goes down. This is a gradual process. During this period, the estrogen level can go up and down. This can cause:

- Hot flushes, night sweats and mood swings
- Vaginal problems such as dryness or itching
- Uncomfortable or painful sexual intercourse.

You may experience these symptoms if you have had your ovaries taken out in an operation.

How Evorel Conti works – both hormones in the patch are continuously released. Evorel Conti patches replace the estrogen that is normally released by the ovaries. However, in women who have a womb, taking an estrogen hormone regularly may cause thickening of the lining of the womb.

- This means it is necessary to add a progestogen hormone to the estrogen
- This supplement helps shed the thickened lining of the womb and prevent problems from happening.

Most women do not have a regular monthly period with Evorel Conti. However, bleeding or spotting does usually occur in the first few months until the treatment settles down.

Evorel Conti 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.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredients or to any of the additional ingredients contained in the medicine (see 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), such as in the legs (deep vein thrombosis) or a blood clot that has traveled to your lungs (pulmonary embolism)
- You have problems with your blood which increases 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

Do not use the preparation if any of the above conditions apply to you. If you are uncertain, consult the doctor or pharmacist before using Evorel Conti.

Special warnings regarding use of the medicine

Medical check-ups

Before taking hormone replacement therapy such as Evorel Conti, 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.

Please 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 or have any of the following conditions. You may need periodic medical check-ups more frequently.

- A problem caused by growth of the womb lining
 - Inside the womb – fibroids
 - Outside the womb – endometriosis
 - Thickening of the lining of the womb (endometrial hyperplasia)
- Increased risk of blood clots (see “Blood clots” later in this section)
- A family history of increased risk of cancer tumors related to estrogen (see “Breast cancer” later in this section), e.g., **mother, sister or grandmother** who had breast cancer
- Hypertension. The doctor may tell you to stop using Evorel Conti if your blood pressure goes up
- Diabetes
- Gallstones
- Migraine or severe headaches
- Systemic lupus erythematosus (SLE), an allergic condition that causes joint pain, skin rash and fever
- Epilepsy
- Asthma
- A disease affecting the eardrum and hearing (otosclerosis)
- A liver disorder, such as a benign liver tumor
- Fluid retention due to 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
- Thyroid 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 to use Evorel Conti, but you should consult the doctor before starting treatment. Tell the doctor if these conditions recur or get worse during the course of treatment with Evorel Conti.

The risk of use of hormone replacement therapy in cases of premature menopause may be different. Consult the doctor regarding the risks.

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

- Any of the conditions mentioned above in section 2 – “Do not use the medicine if”
 - Yellowing of the skin or the whites of the eyes (jaundice). These may be signs of a liver disease
 - A notable rise in 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)”

Smoking

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

Children and adolescents

The medicine is not intended for use in children.

Operations or check-ups

Inform the doctor if you are going to have surgery. You may need to stop using the HRT 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 this kind of preparation.

If you perform a urine or blood test in a hospital or at the family doctor, please tell them that you are using Evorel Conti. This is because Evorel Conti 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.
- Medicines for tuberculosis such as: rifampicin or rifabutin.
- Medicines for treatment of HIV infection such as nevirapine, efavirenz, ritonavir and nelfinavir.
- Medicine for treatment of hepatitis C – telaprevir.
- Bosentan – a medicine for high blood pressure in the blood vessels of the lungs.
- St. John’s wort – for depression.

Taking these medicines with Evorel Conti may stop its activity, 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 Conti and lamotrigine could affect the control of your epilepsy.

Pregnancy and breastfeeding

Do not use the preparation if you are pregnant, think you may be pregnant or might be pregnant. This is because Evorel Conti may affect the baby.

Evorel Conti is intended for women after menopause only. If you become 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 Conti affects the ability to drive or use machines. 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 HRTs bears some risks. Consider the following information before starting use of, or when continuing treatment with of HRTs.

The effect of hormone replacement therapy on the heart and blood circulation

Heart diseases (heart attack)

Hormone replacement therapy is **not recommended** for women who have recently had heart diseases. If you have ever had a heart disease, talk to the doctor to determine whether or not you should use these preparations.

Hormone replacement therapy will not help to prevent heart diseases.

Women over the age of 60 years who use estrogen-progestogen HRT are slightly more likely to develop heart disease than women not being treated with these preparations.

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

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

The chest pain may be a sign of heart disease.

Stroke

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

Other factors may increase the risk of stroke:

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

If you are worried about any of the above-mentioned factors, 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?

The risk of getting a stroke is 1.5 times higher in women using HRT compared to women not using such a preparation. The number of extra cases in women using HRT is higher as age increases.

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

- 8 out of 1000 women not taking an HRT** are expected to have a stroke
- 11 out of 1000 women taking an HRT** are expected to have a stroke (3 extra cases)

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

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

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

Blood clots in a vein (thrombosis)

Hormone replacement therapy may increase the risk of formation of blood clots in the veins (DVT – deep vein thrombosis). The risk of formation of blood clots in the veins is 1.3-3 times higher in women using HRT as compared to women not using these preparations, especially during the first year of using them.

These blood clots are not always serious. However, if such a blood clot travels to the lungs, chest pain, breathlessness, collapse and even death may occur. This condition is called pulmonary embolism.

There is a higher likelihood of getting a blood clot:

- If you are overweight (BMI above 30 kg/m²)
- With increased age
- If you have suffered from a blood clot in the past
- If you have cancer
- If you are taking medication containing an estrogen
- If any of your relatives have suffered from blood clots
- If you are pregnant or have just had a baby
- 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 long period of time because of surgery, injury or illness
- If you are about to go on a long journey, during which you will not be moving about for some time
- If you have a rare illness called systemic lupus erythematosus (SLE)

If any of the conditions mentioned above apply to you, talk to the doctor whether to take an HRT.

How likely is a blood clot?

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

- 4-7 out of 1000 women not taking an HRT** are expected to have a blood clot
- 9-12 out of 1000 women taking an HRT containing estrogen and progestogen** are expected to have a blood clot (5 extra cases)

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

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

These may be signs of formation of a blood clot.

HRT and cancer

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 the **following changes in your breast**, such as:

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

Make an appointment with the doctor as soon as possible.

Additionally, you are advised to join mammography screening programs when offered to you. Inform the healthcare professional who is actually taking the x-ray that you use HRT, as these preparations 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.

Endometrial hyperplasia and endometrial cancer

Taking estrogen-only hormone replacement therapy for a long time may increase the risk of endometrial cancer. Taking progestogen in addition to the 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 as separate preparations, or as a combined hormone replacement preparation.

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 an HRT that includes progestogen in addition to estrogen.

Evorel Conti is a hormone replacement preparation that contains estrogen and progestogen.

How likely is endometrial cancer?

Looking at women aged 50-65 who have not undergone a hysterectomy, on average:

- 5 out of 1000 women not taking a hormone replacement therapy** will get endometrial cancer
- In women taking an estrogen-only HRT, 10-60 women out of 1000** will get endometrial cancer (**between 5 and 55 extra cases**), depending on the dosage and duration of treatment.

The addition of progestogen to an estrogen-only HRT 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 using HRTs.

But if the bleeding or spotting:

- Carries on for more than the first few months of use
 - Starts after you have been on the HRT for some period
 - Carries on even after you have stopped taking the HRT
- 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 a slightly higher 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 (1 extra case).

Dementia

Evorel Conti and other similar medicines will not stop memory loss (dementia). Women who start using medicines like Evorel Conti 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 a new pack of Evorel Conti immediately after finishing the previous pack, without a break between packs.

The doctor is aiming to reduce the symptoms with the lowest dosage for the shortest amount of time.

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

When to start treatment with Evorel Conti

Treatment can be started at any time if:

- You have not been using another HRT

Put an Evorel Conti 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 menstrual bleeding

If you are using another HRT:

- The day to start Evorel Conti treatment will depend on the other type of HRT you have been using.

Please refer to the doctor if you are not sure which type of HRT you are using.

Changing the Evorel Conti 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 on the same two days every week. This will mean that one patch is on for three days and the second patch for four days.
- For example, if you applied your first patch on a Monday, put on the second patch on Thursday and again on the following Monday. You can work out 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

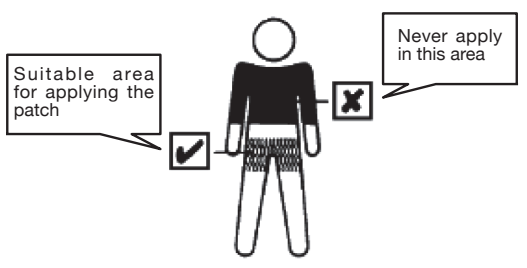
To help you remember your two patch change days, mark them on the back of the pack. They are written on the pack like this:



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 on skin which has been recently treated with cream, moisturizer or talc
- 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 taking it out of the protective pouch

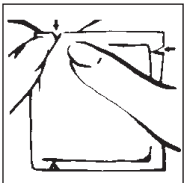


Applying a patch

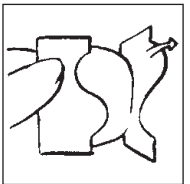
Do not use a patch if the protective pouch is already open.

Step 1: Open and Peel

- Using the notches as a guide, tear along the 2 edges of the pouch and 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.

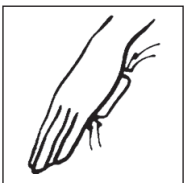


Step 2: Apply and Press

- 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 into the toilet bowl.



After removing the patch, a little glue may remain on your skin. The glue will disappear over time, or baby oil can be used to remove the remaining 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 the doctor if you need more patches.

If you forget to change the patch

Change the patch as soon as you remember and then continue with your regular change days. 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 Conti than recommended

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

- Painful or tender breasts
- Nausea or vomiting
- Unexpected vaginal bleeding
- Feeling depressed
- Tiredness
- Acne
- Growth of body or facial hair

These symptoms, which are due to excess estrogen or progestogen, are reversible upon removal of the patch. Consult the doctor or pharmacist before using another patch.

Contraception while using Evorel Conti

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

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

Everyday activities

- You can shower or take a bath as normal. Do not scrub the skin around the patch too hard, as this can 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 a tight garment or rubber bands.
- You can sunbathe, but be sure to keep the patch under a garment, out of direct sunlight.

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, please consult with the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Evorel Conti 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.

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, rapid swelling of the hands and feet and stomach cramps
 - Blood clots (thrombosis) (affects less than 1 in 1000 users) or stroke (unknown frequency)
 - 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 100 users)
 - An increase in blood pressure (affects less than 1 in 10 users)
 - Breast or ovarian cancer, endometrial cancer or hyperplasia (long, heavy or irregular menstruation)
 - Widespread rash with skin peeling and blistering in the mouth, eyes and genitals (Stevens-Johnson syndrome) (unknown frequency)
 - Seizures (affects less than 1 in 1000 users)

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

Very common side effects – effects that occur in more than one user in ten