Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) – 1986
This medicine is dispensed with a doctor's prescription only

Eviana
Film-coated tablets

Active ingredients:
estradiol as hemihydrate 0.5 mg
norethisterone acetate 0.1 mg

Inactive ingredients and allergens in this medicine: See section 2 under 'Important information about some of this medicine's ingredients', and 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 condition is similar to yours.

1. What is this medicine intended for?

Eviana is used in women who have a uterus:

- For treatment of moderate to severe vasomotor symptoms that occur when a woman's menstrual cycle stops (menopause).
- For prevention of osteoporosis (bone thinning) in postmenopausal women who are at high risk of fractures in cases where using an estrogen-free treatment for osteoporosis is not suitable.

There is limited experience treating women over 65 years old.

Therapeutic group: combined estrogen and progestagen medicines.

Eviana is a continuous combined hormone replacement therapy (HRT) for postmenopausal women. Eviana contains two types of hormones, an estrogen (estradiol) and a progestogen (norethisterone acetate). During menopause, the level of estrogen in a woman's body drops. This can cause symptoms such as hot face, neck and chest ('hot flashes'). Eviana alleviates these symptoms. The treatment will be given if the symptoms significantly impact your daily life.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredients or to any of the other ingredients in this medicine (see section 6 'Additional information').
- You have, have had or suspect having breast cancer.
- You have, have had or suspect having cancer of the womb lining (cancer of the endometrium), or some other estrogen-dependent cancer.
- You have any unexplained vaginal bleeding.

- You have excessive thickening of the womb lining (endometrial hyperplasia) that is not being treated.
- You have or have ever had a blood clot in a vein (venous thromboembolism), 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 previously 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).

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

Special warnings about using this medicine

Medical history and regular check-ups
The use of hormone replacement therapy (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 you 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 using Eviana you must be checked regularly by your doctor (at least once a year). At these check-ups, discuss with your doctor the benefits and risks of continuing to use Eviana.
You must have regular breast screening, as recommended by your doctor.

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

- fibroids (myomas) 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 (venous thromboembolism)')
- increased risk of getting an estrogen-sensitive cancer (for example having a mother, sister or grandmother who has had breast cancer)
- high blood pressure
- a liver disorder, such as a benign liver tumor
- 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 fats in your blood (triglycerides)
- fluid retention due to heart or kidney problems
- a condition where your thyroid gland fails to produce enough thyroid hormone (hypothyroidism) and you are treated with thyroid hormone replacement therapy
- a hereditary condition causing recurrent episodes of severe swelling (hereditary angioedema) or if you have had episodes of rapid swelling of the hands, face, feet, lips, eyes, tongue, throat (airway blockage) or digestive tract (acquired angioedema)
- lactose intolerance.

Note - Eviana 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 estrogen-only HRT increases the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer). The progestagen in Eviana protects you from this increased risk.

Compare
In women who still have a womb and who are not using HRT, on average, 5 of 1,000 will be diagnosed with cancer of the womb lining at age 50 to 65.
In women aged 50 to 65 who still have a womb and who are using estrogen-only HRT, on average, between 10 to 60 women out of 1,000 will be diagnosed with cancer of the womb lining (this means 5 to 55 additional cases) depending on dose and how long used.

Irregular bleeding
You may have irregular bleeding or drops of blood (spotting) during the first 3-6 months of taking Eviana. However, if the irregular bleeding:
- carries on for more than the first 6 months
- starts after you have been taking Eviana for more than 6 months
- carries on after you have stopped taking Eviana,

consult your doctor as soon as possible.

Breast cancer
Evidence shows that taking combined estrogen-progestagen or estrogen-only HRT increases the risk of breast cancer. The additional risk depends on how long you use HRT. The additional risk becomes clear within 3 years of use. After stopping therapy, the increased risk decreases with time, but it may persist for 10 years or more if you have used HRT for more than 5 years.

Compare
In 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 estrogen-only HRT for 5 years, there will be 16-17 cases in 1,000 users (this means 0 to 3 additional cases).
For women aged 50 who start taking combined estrogen-progestagen HRT for 5 years, there will be 21 cases in 1,000 users (this means 4 to 8 additional cases).

In women aged 50 to 59 who are not taking HRT, on average, 27 in 1,000 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 1,000 users (this means 7 additional cases).
For women aged 50 who start taking combined estrogen-progestagen HRT for 10 years, there will be 48 cases in 1,000 users (this means 21 additional 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 have a mammography screening if 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 estrogen-only or combined estrogen-progestagen 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 using HRT, about 2 women in 2,000 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 2,000 users (this means about 1 additional case).

Effect of HRT on heart and circulation

Blood clots in a vein (venous thromboembolism)
The risk of **blood clots in the veins** is about 1.3 to 3 times higher in women using HRT than in women not using HRT, especially during the first-year use.
Blood clots can be serious, and if a blood clot reaches the lungs, it can cause chest pain, breathlessness, fainting and even death.
You are more likely to get a blood clot in your veins as you get older and also if any of the following applies to you. Inform your doctor if:
- 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 a 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 section 4 under 'Stop taking Eviana and see a doctor immediately'.

<u>Compare</u>
Looking at women in their 50s who are not using 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 estrogen-progestagen HRT for over 5 years, there will be 9 to 12 cases in 1,000 users (this means an additional 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 estrogen-progestagen HRT are slightly more likely to develop heart disease than those not taking any HRT.

Stroke
The risk of getting stroke is about 1.5 times higher in women using HRT than in women not using it. 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 using HRT, on average, 8 in 1,000 would be expected to have a stroke over a 5-year period.
For women in their 50s who are using HRT, there will be 11 cases in 1,000 users over 5 years (this means an additional 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.

Smoking
If you smoke, do not use this medicine without consulting your doctor first. You are advised to stop smoking when you use a combined hormonal product such as Eviana. If you are unable to stop smoking and you are over 35, consult your doctor.

Tests and follow-up
If you need to have a blood test, tell your doctor or the lab staff that you are taking Eviana, because this medicine can affect the results of certain tests.

Interactions with other medicines
If you are taking or have recently taken other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist.
Some medicines may interfere with the effect of Eviana. This might lead to irregular bleeding. This applies to the following medicines:
- medicines for **epilepsy** (such as phenobarbital, phenytoin and carbamazepine)
- medicines for **tuberculosis** (such as rifampicin and rifabutin)
- medicines for **human immunodeficiency virus (HIV) infection** (such as nevirapine, efavirenz, ritonavir and nelfinavir)
- medicines for **hepatitis C infections** (such as telaprevir)
- 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 regimen with glecaprevir/pibrentasvir) may cause increases in liver function blood test results (increase in ALT liver enzyme) in women using combined hormonal contraceptives (CHCs) containing ethinylestradiol. Eviana contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Eviana with the HCV combination regimen. Consult your doctor.

Other medicines may increase the effects of Eviana:
- medicines containing **ketoconazole** (a fungicide)

Eviana may have an impact on a concomitant treatment with cyclosporine.

Using this medicine and food
The tablets can be taken with or without food and drink.

Pregnancy and breastfeeding
Pregnancy: Eviana is for use only in women who have stopped menstruating. If you become pregnant, stop taking Eviana and contact your doctor.
Breastfeeding: Do not use Eviana if you are breastfeeding.

Driving and using machines
Eviana has no known effect on the ability to drive or use machines.

Important information about some of this medicine's ingredients
Eviana contains lactose monohydrate. If you have an intolerance to some sugars, contact your doctor before taking Eviana.

3. How to use this medicine?

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

Take one tablet, once a day, at about the same time each day. Take the tablet with a glass of water.
Do not exceed the recommended dose.
Take a tablet every day without stopping. Once you have used all the 28 tablets in the monthly pack, continue immediately with the next pack. For further information on the use of the calendar pack, see User Instructions at the end of the package leaflet.

You may start using Eviana on any convenient day. However, if you are switching from another HRT product when you have your monthly bleeding, start your treatment straight after the bleeding has stopped.
Your doctor should prescribe the lowest dose to treat your symptom for a period that is as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

There are no studies about the rate of absorption, efficacy, and safety of tablets that are split or crushed, so splitting or crushing these tablets cannot be recommended.

If you have accidentally taken a higher dose
If you have taken a larger dose of Eviana than required, talk to a doctor or pharmacist as soon as possible. Taking a larger dose of estrogens than your doctor prescribed may cause breast tenderness, nausea, vomiting, and/or irregular vaginal bleeding. Taking a larger dose of progestagens than your doctor prescribed may cause depressive mood, fatigue, acne, or growth of body or facial hair.
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine

If you forget to take your tablet at the usual time, take it within the next 12 hours. If more than 12 hours have gone by, start again as normal the next day. Do not take a double dose to make up for a forgotten tablet.
Missing a dose may increase the likelihood of breakthrough bleeding and spotting, unless you have had your womb removed.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

If you stop taking this medicine
If you would like to stop taking Eviana, talk to your doctor first. Your doctor will explain the effects of stopping treatment and discuss other possibilities with you.

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

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take 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

As with any medicine, using Eviana may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of 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
- probable memory loss if HRT is started over the age of 65.

For more information about these side effects, see section 2, 'Before using this medicine'.

Stop taking Eviana and see a doctor immediately
If you notice any of the following effects when you take HRT:
- any of the conditions listed under 'Do not use this medicine if'
- yellowing of your skin or the white part of your eyes (jaundice). These may be signs of a liver disease
- swollen face, tongue and/or throat and/or difficulty swallowing or hives (skin rash), together with difficulty breathing, which are suggestive of an angioedema
- a large rise in your blood pressure (symptoms can be headache, tiredness, dizziness)

- migraine-like headaches, happening 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 breathing

For additional information see section 2 under 'Blood clots in a vein (venous thromboembolism)'.

Very common side effects (may affect more than 1 in 10 women)
- vaginal bleeding.

Common side effects (may affect up to 1 in 10 women)
- fungal infections of the genitals or a vaginal inflammation
- excessive thickening of the lining of the womb (endometrial hyperplasia)
- nausea
- abdominal (stomach) pain
- back or neck pain
- pain in the arms or legs
- headache.

Uncommon side effects (may affect up to 1 in 100 women)
- allergic reaction (hypersensitivity)
- depression or worsening of existing depression
- nervousness
- dizziness
- migraine (see 'Stop taking Eviana' in section 4)
- breast pain or breast discomfort
- abdominal (stomach) swelling or discomfort
- weight gain caused by fluid retention
- swelling of arms and legs (peripheral edema)
- leg cramps
- heartburn (dyspepsia)
- acne
- hair loss (alopecia)
- itching or urticaria (skin rash).

Very rare side effects (may affect up to 1 in 10,000 women)
Generalized hypersensitivity reactions have been reported (for example anaphylactic reaction/shock)

Other side effects of combined HRT
- 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)
  - red or purple discolorations of the skin and/or mucous membranes (vascular purpura)
- dry eyes
- changes in composition of tear fluid.

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.

Reporting side effects
You can report side effects to the Ministry of Health by following the 'Reporting Side Effects of Drug Treatment' link on the Ministry of Health home page (www.health.gov.il), which opens an online form for reporting side effects, or 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 your doctor.
Do not use the medicine after the expiry date (exp. date) which is stated on the label and the outer carton. The expiry date refers to the last day of that month.

Storage conditions
Store below 25°C. Do not refrigerate.
Keep the container in the outer carton in order to protect it from light.

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

6. Additional information

In addition to the active ingredients, this medicine also contains:
lactose monohydrate, maize starch, hydroxypropylcellulose, hypromellose, talc, magnesium stearate and triacetin.

What the medicine looks like and contents of the pack:
The film-coated tablets are white, round with a diameter of 6 mm. The tablets are engraved with NOVO 291 on one side and the Novo Nordisk logo (an Apis bull) on the other side.
Pack size: 28 film-coated tablets.

Registration holder's name and address:
Novo Nordisk Ltd., 1 Atir Yeda St., Kfar-Saba, 4464301

Manufacturer's name and address:
Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark

Revised in November 2023 according to Ministry of Health guidelines.

Registration number of the medicine in the Ministry of Health's National Drug Registry: 139-85-31685.

User Instructions

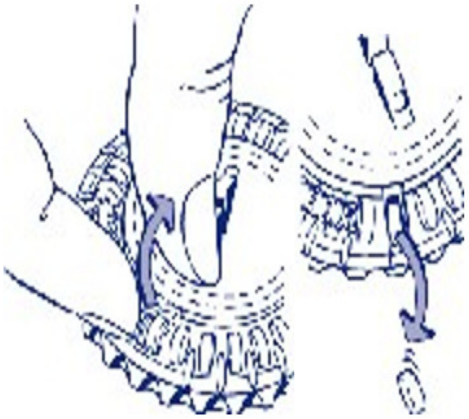
How to use the calendar pack

1. Set the day reminder

Turn the inner disc to set the day of the week opposite the little plastic tab.

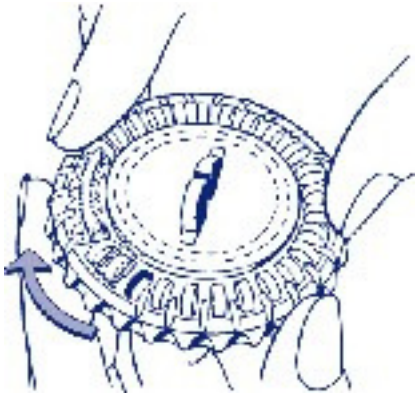
2. Take the first day's tablet

Break the plastic tab and tip out the first tablet.



3. Move the dial every day

On the next day, simply move the transparent dial clockwise one space as indicated by the arrow. Tip out the next tablet. Remember to take only one tablet once a day.
You can only turn the transparent dial after the tablet in the opening has been removed.



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