

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

This medicine is dispensed with a doctor's prescription only

Activelle®

Film-coated tablets

Active ingredients:

Each film-coated tablet contains:

Estradiol (as hemihydrate) 1 mg

Norethisterone acetate 0.5 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 medical condition is similar to yours.

1. What is this medicine intended for?

Activelle is intended for:

- Relief of symptoms that are due to a drop in the level of the hormone estrogen in postmenopausal women, when at least one year has passed since their last natural period.
- Prevention of osteoporosis (bone thinning) in menopausal women who are at high risk of future fractures and who cannot be treated with other medicines for this condition.

There is only limited experience of treating women older than 65.

Therapeutic group: progestagens and estrogens; combined therapy.

Activelle is a continuous combined hormone replacement therapy (HRT). It contains two types of female hormones, estrogen and progestagen. During the menopause, the amount of estrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ('hot flushes'). Activelle alleviates these symptoms after menopause. You will only be prescribed Activelle if your symptoms seriously hinder your daily life.

Activelle is prescribed for women who have not had their womb removed, and whose periods stopped more than a year ago.

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 (listed in section 6 'Additional information').
- You have, have had, or suspect having **breast cancer**.
- You have, or have had **cancer which is sensitive to estrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it.
- You have **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** (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 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 appear for the first time while you are taking Activille, 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 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 Activille 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 Activille.

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

Before you start treatment with Activille, tell your doctor if you have ever had any of the following problems, as they may return or become worse during treatment with Activille. 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 estrogen-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 tumor
- diabetes
- gallstones
- migraines 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
- lactose intolerance.

Stop taking Activelle and see a doctor immediately

If you notice any of the following conditions while you are taking HRT:

- any of the conditions mentioned in the 'Do not use this medicine if'
- 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 in swallowing or hives (skin rash), 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: Activelle 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 Activelle protects you from this increased risk.

Irregular bleeding

You may have irregular bleeding or drops of blood (spotting) during the first 3-6 months of taking Activelle.

However, if the irregular bleeding:

- carries on for more than the first 6 months
- starts after you have been taking Activelle for more than 6 months
- carries on after you have stopped taking Activelle

consult your doctor as soon as possible.

Breast cancer

Evidence shows that taking combined estrogen-progestagen 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.

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 estrogen-only HRT for 5 years, there will be 16-17 cases in 1,000 users (i.e. an extra 0 to 3 cases).

For women aged 50 who start taking estrogen-progestagen 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 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 (i.e. an extra 7 cases).

For women aged 50 who start taking estrogen-progestagen HRT for 10 years, there will be 48 cases in 1,000 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 undergo mammography screening. 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 taking 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 (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 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 situations 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 (body mass index [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 'Stop taking Activelle and see a doctor immediately'.

Compare

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 estrogen-progestagen HRT for over 5 years, there will be 9 to 12 cases in 1,000 users (i.e. 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 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 HRT users than in non-users. The number of extra cases of stroke due to use of HRT increase with age.

Compare

Looking at women in their 50s who are not taking 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 taking HRT, there will be 11 cases in 1,000 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.

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 Activelle. If you are unable to stop smoking and you are over 35, consult your doctor.

Tests and follow-up

If you need a blood test, tell your doctor or the laboratory staff that you are taking Activelle, 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. Particularly if you are taking:

Some medicines may interfere with the effect of Activelle. 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 **HIV infections** (such as nevirapine, efavirenz, ritonavir and nelfinavir)
- Medicines for **hepatitis C infections** (such as telaprevir)
- 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 combinations regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir) may cause increases in liver function blood test results (increase in ALT liver enzyme) in women using Combined Hormonal Contraceptives (CHCs) containing ethinylestradiol. Activelle contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Activelle with this HCV combination regimen.

Other medicines may increase the effects of Activelle:

- Medicines containing **ketoconazole** (a fungicide).

Activelle 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

Activelle is for use in postmenopausal women only. If you become pregnant, stop taking Activelle and contact your doctor. Do not take Activelle if you are breastfeeding.

Driving and using machines

Activelle has no known effect on the ability to drive or use machines.

Important information about some of this medicine's ingredients

Activelle contains lactose monohydrate. If you have an intolerance to some sugars, contact your doctor before taking Activelle.

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 (swallow) once a day, at about the same time every day. Once you have finished all the 28 tablets in the pack, start a new pack continuing the treatment without interruption. For further information on the use of the calendar pack, see 'User Instructions' at the end of the package leaflet.

You may **start treatment with Activelle** on any convenient day. However, if you are switching from another HRT product when you have monthly bleeding, start your treatment straight after the bleeding has ended.

Your doctor should aim to prescribe the lowest dose to treat your symptoms for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

Do not exceed the recommended dose.

There is no information about crushing/splitting, so this practice is not recommended.

If you have accidentally taken a higher dose

An overdose of Activelle could cause nausea or vomiting. 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, skip the missed dose and start again as normal the next day. Do not take a double dose to make up for a forgotten tablet. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting if you still have a womb.

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 Activelle, 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 Activelle. You may need to stop taking Activelle about 4 to 6 weeks before the operation to reduce the risk of a blood clot (see section 2, 'Blood clots in a vein (thrombosis)'). Ask your doctor when you can start taking Activelle again.

Do not take medicines in the dark! Check the label and dose every time 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 Activelle 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
- 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'.

Hypersensitivity/allergy (uncommon side effect – may affect 1 to 10 in 1,000 users)

Though it is an uncommon event, hypersensitivity/allergy may occur. Signs of hypersensitivity/allergy may include one or more of the following symptoms: hives (skin rash), itching, swelling, difficulty in breathing, low blood pressure (paleness and coldness of skin, rapid heart beat), feeling dizzy, sweating, which could be signs of anaphylactic reaction/shock. If one of the mentioned symptoms appears, **stop taking Activelle and seek immediate medical help.**

Very common side effects (affect more than 1 in 10 users)

- Breast pain or breast tenderness
- Vaginal bleeding.

Common side effects (affect 1 to 10 in 100 users)

- Headache
- Weight gain caused by fluid retention
- Vaginal inflammation
- Migraine, new or worse than before
- Vaginal infection with a fungus
- Depression, new or worse than before
- Nausea
- Enlargement or swelling of the breasts (breast edema)
- Back pain
- Uterine fibroid (benign tumor), aggravation, occurrence or reoccurrence
- Swelling of arms and legs (peripheral edema)
- Weight increase.

Uncommon side effects (affect 1 to 10 in 1,000 users)

- abdominal bloating, abdominal pain, abdominal discomfort or flatulence
- Acne
- Hair loss
- Abnormal (male pattern) hair growth
- Itching or hives (urticaria)
- Inflammation of a vein (Inflammation of the superficial veins)
- Leg cramps
- Drug ineffective
- Allergic reaction
- Nervousness.

Rare side effects (affect 1 to 10 in 10,000 users)

- blood clots in the blood vessels of the legs or the lungs (deep vein thrombosis, lung embolism).

Very rare side effects (affect less than 1 in 10,000 users)

- Cancer of the lining of the womb (endometrial cancer)
- Excessive thickening of the lining of the womb (endometrial hyperplasia)
- Increase in blood pressure or worsening of high blood pressure
- Gall bladder disease, gall stones occurrence/reoccurrence or aggravated
- Excessive secretion of sebum, skin eruption
- Acute or recurring attack of edema (angioneurotic edema)
- Insomnia, dizziness, anxiety
- Change in sexual desire
- Visual disturbances
- Weight decreased
- Vomiting
- Heartburn
- Vaginal and genital itching
- Heart attack and stroke.

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).

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.

Store the container in the outer carton in order to protect it from light. Keep away from heat.

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, copovidone, talc, magnesium stearate.

The tablet film-coating contains: hypromellose, glycerol triacetate, talc.

What the medicine looks like and contents of the pack:

The film-coated tablets are white, round, biconvex with a diameter of 6 mm. The tablets are engraved 'NOVO 288' on one side and the Novo Nordisk logo (an Apis bull) on the other side. Pack size: 28 film-coated tablets in a calendar pack.

Registration holder's name and address:

Novo Nordisk Ltd., 1 Atir Yeda Street, Kfar-Saba, 4464301.

Manufacturer's name and address:

Novo Nordisk A/S, Novo Allé 1, DK-2880 Bagsværd, Denmark.

Revised in July 2025.

Registration number of the medicine in the National Drug Registry of Ministry of Health's:
114-30-29629

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User Instructions

How to use the calendar pack

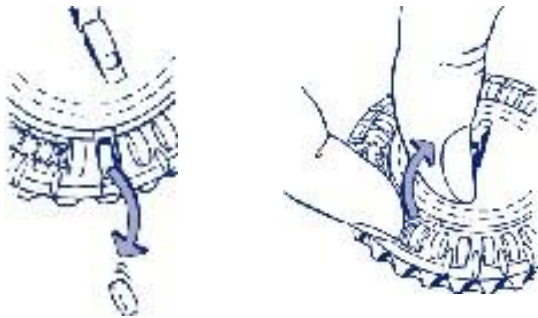
1. Set the day reminder

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



2. How to 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 1 space as indicated by the arrow. Tip out the next tablet. Remember to take only 1 tablet every day.

You can only turn the transparent dial after the tablet in the opening has been removed.

