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:
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 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; continuous, combined therapy.

Activelle is a continuous combined hormone replacement therapy (HRT). It contains two types of female hormones, estrogen and progestagen.
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 this type of cancer.
- 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 have previously 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).

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If any of the above conditions appear for the first time while you are taking Activelle, 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 taking Activelle 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 to use Activelle.

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

Before you start treatment with Activelle, tell your doctor if you have ever had any of the following problems, as they may return or become worse during treatment with Activelle. If so, you should see your doctor more often for periodic 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 [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 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 heart or kidney problems
- hereditary and acquired angioedema
- lactose intolerance.

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 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 HRT, the additional 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 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
- lumps you can see or feel.

Additionally, you are advised to undergo mammogram 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 and 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 (this means about one additional case).

Effect of HRT on heart and circulation

Blood clots in the veins (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 of using this medicine.
Blood clots can be serious, and if a blood clot travels to 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 conditions apply 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>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 '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 combined estrogen and 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 women 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 additional cases of stroke due to use of HRT increases 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 taking 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 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 lab 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 medications and dietary supplements, tell your doctor or pharmacist.
Certain 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)
- herbal remedies containing **St. John's wort** (*Hypericum perforatum*)
- medicines for **hepatitis C infections** (such as telaprevir).

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

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 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. Consult your doctor.

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, consult 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, 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 using Activelle 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 will prescribe the lowest dose to treat your symptoms for as short a period as possible. 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 scheduled 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. Missing 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 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 Activelle 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 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 taking this treatment:
- 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'.

Stop taking Activelle and see a doctor immediately
If you notice any of the following conditions while you are taking HRT:
- any of the medical problems listed under 'Do not use this medicine if'
- yellowing of the skin or the whites of the eyes (jaundice). These may be signs of a liver disease.
- swelling of the face, tongue and/or throat and/or difficulty in swallowing or hives (skin rash) with difficulty in breathing, which could indicate angioedema

- significant increase in blood pressure (possible symptoms are headache, fatigue, dizziness)
- migraine-like headaches that 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 (venous thromboembolism)'.

Hypersensitivity/allergy (uncommon side effect – may affect 1 to 10 in 1,000 users)
Although 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 (pale and cold skin, fast heart rate), dizziness, sweating, which could be signs of anaphylactic reaction/shock. If you get any of the symptoms mentioned, **stop taking Activelle and seek immediate medical help.**

Very common side effects (affect more than 1 in 10 users)
- breast pain or 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
- aggravation, occurrence or reoccurrence of a uterine fibroid (benign tumor)
- swelling of arms and legs (peripheral edema)
- weight gain.

Uncommon side effects (affect 1 to 10 in 1,000 users)
- abdominal bloating, abdominal pain, abdominal discomfort or flatulence
- acne
- hair loss (alopecia)
- abnormal (male pattern) hair growth
- itching or hives (urticaria)
- inflammation of a vein (superficial thrombophlebitis)
- leg cramps
- medicine is 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 womb lining (endometrial hyperplasia)
- increase in blood pressure or worsening of high blood pressure
- gall bladder disease, gall stones occurrence/reoccurrence or aggravated gallstones
- excessive secretion of sebum, skin eruption
- acute or recurring attack of edema (angioneurotic edema)

- insomnia, dizziness, anxiety
- change in sexual desire
- visual disturbances
- weight loss
- 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 coating contains: hypromellose, glycerol triacetate, talc.

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 288" on one side and the Novo Nordisk logo (a bull) on the other side.
Pack size: 28 film-coated tablets in a calendar pack marked with the days of the month.

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, DK-2880 Bagsværd, Denmark.

Revised in January 2024.

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

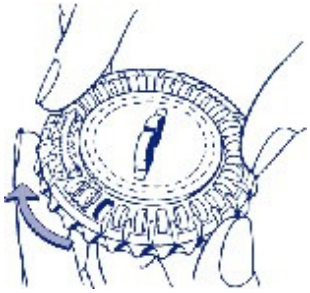
User Instructions

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



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