Package leaflet: Information for the user

Activelle 1 mg/0.5 mg film-coated tablets
estradiol/norethisterone acetate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Activelle is and what it is used for

Activelle is a continuous combined Hormone Replacement Therapy (HRT). It contains two types of female hormones, an oestrogen and a progestagen. Activelle is used in postmenopausal women with at least 1 year since their last natural period.

Activelle is used for:

Relief of symptoms occurring after menopause
During the menopause, the amount of oestrogen 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.

Prevention of osteoporosis
After the menopause some women may develop fragile bones (osteoporosis). You should discuss all available options with your doctor.
If you are at an increased risk of fractures due to osteoporosis and other medicines are not suitable for you, you can use Activelle to prevent osteoporosis after menopause.

Activelle is prescribed for women who have not had their womb removed, and whose periods stopped more than a year ago.
There is only limited experience of treating women older than 65 years with Activelle.

2. What you need to know before you take Activelle

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 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 with Activelle.

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

Do not take Activelle
If any of the following applies to you. If you are not sure about any of the points below, **talk to your doctor** before taking Activelle.
Do not take Activelle:
- If you have, have had or suspect having **breast cancer.**
- If you have, or have had **cancer which is sensitive to oestrogens,** such as cancer of the womb lining (endometrium), or if you are suspected of having it.
- If you have any **unexplained vaginal bleeding.**
- If you have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated.
- If 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).
- If you have a **blood clotting disorder** (such as protein C, protein S or antithrombin deficiency).
- If you have or previously have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke** or **angina.**
- If you have or have ever had a **liver disease** and your liver function tests have not returned to normal.
- If you have a **rare blood problem called 'porphyria'** which is passed down in families (inherited).
- If you are **allergic** (hypersensitive) to **estradiol**, **norethisterone acetate** or any of the other ingredients of Activelle (listed in section 6 'Contents of the pack and other information').

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

Warnings and precautions
Tell your doctor if you have ever had any of the following problems, before you start the treatment, as these may return or become worse during treatment with Activelle. 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 a oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer)
- high blood pressure
- a liver disorder, such as a benign liver tumour
- diabetes
- gallstones
- migraine or severe headaches

- a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE)
- epilepsy
- asthma
- a disease affecting the eardrum and hearing (otosclerosis)
- a very high level of fat in your blood (triglycerides)
- fluid retention due to cardiac or kidney problems
- hereditary and acquired angioedema
- lactose intolerance.

Stop taking Activelle and see a doctor immediately
If you notice any of the following when taking HRT:
- any of the conditions mentioned in the 'Do not take Activelle' section
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease
- swollen face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing which are suggestive of an angioedema
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness)
- migraine-like headaches which happen for the first time
- if you become pregnant
- if you notice signs of a blood clot, such as:
  - painful swelling and redness of the legs
  - sudden chest pain
  - difficulty in breathing.

  For more information, see 'Blood clots in a vein (thrombosis)'.

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 oestrogen-only HRT will increase the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer).

The progestagen in Activelle protects you from this extra 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

see your doctor as soon as possible.

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

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 oestrogen-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 oestrogen-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 oestrogen-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 oestrogen-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 join mammography screening programs when offered to you. For mammogram screening, it is important that you inform the nurse/healthcare professional who is actually taking the x-ray that you use HRT, as this medication may increase the density of your breasts which may affect the outcome of the mammogram. Where the density of the breast is increased, mammography may not detect all lumps.

Ovarian cancer
Ovarian cancer is rare - much rarer than breast cancer. The use of oestrogen-only or combined oestrogen-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 applies to you. Inform your doctor if any of these situations applies to you:
- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, 'If you need to have surgery')
- you are seriously overweight (BMI >30 kg/m^2)
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots
- if 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 oestrogen-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 oestrogen-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 will 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.

Using other medicines
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)
- 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. Your doctor will advise you.

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

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

Laboratory tests
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 some tests.

Taking Activelle with food and drink
The tablets can be taken with or without food and drink.

Pregnancy and breast-feeding

Pregnancy: Activelle is for use in postmenopausal women only. If you become pregnant, stop taking Activelle and contact your doctor.

Breast-feeding: You should not take Activelle if you are breast-feeding.

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

Important information about some of the ingredients in Activelle:
Activelle contains lactose monohydrate. If you have an intolerance to some sugars, contact your doctor before taking Activelle.

3. How to take Activelle

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are unsure.

Take one tablet once a day, at about the same time each 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 an 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 symptom for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

If you take more Activelle than you should
If you have taken more Activelle than you should, talk to a doctor or pharmacist. An overdose of Activelle could make you feel sick or vomit.

If you forget to take Activelle
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 your womb.

If you stop taking Activelle
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 have any further questions on the use of this medicine, ask your doctor or pharmacist.

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.

4. Possible side effects

Like all medicines, this medicine can have side effects, although not everybody gets 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, 'What you need to know before you take Activelle'.

Hypersensitivity/allergy (uncommon side effect – affects 1 to 10 users in 1,000)
Though it is an uncommon event, hypersensitivity/allergy may occur. Signs of hypersensitivity/allergy may include one or more of the following symptoms: hives, 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 (affects more than 1 user in 10)
- Breast pain or breast tenderness
- Vaginal bleeding.

Common side effects (affects 1 to 10 users in 100)
- 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 oedema)
- Back pain
- Uterine fibroid (benign tumour), aggravation, occurrence or reoccurrence
- Swelling of arms and legs (peripheral oedema)
- Weight increase.

Uncommon side effects (affects 1 to 10 users in 1,000)
- Bloating, abdominal pain, swelling, discomfort or flatulence
- Acne
- Hair loss (alopecia)
- Abnormal (male pattern) hair growth
- Itching or hives (urticaria)
- Inflammation of a vein (superficial thrombophlebitis)
- Leg cramps
- Drug ineffective
- Allergic reaction
- Nervousness.

Rare side effects (affects 1 to 10 users in 10,000)
- Blood clots in the blood vessels of the legs or the lungs (deep vein thrombosis, lung embolism).

Very rare side effects (affects less than 1 user in 10,000)
- 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 oedema (angioneurotic oedema)
- 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)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:
HPRA Pharmacovigilance
Website: www.hpra.ie
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Activelle

Keep this medicine out of the sight and reach of children.

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

Do not store above 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. Contents of the pack and other information

What Activelle contains

– The active substances are estradiol 1 mg (as estradiol hemihydrate) and norethisterone acetate 0.5 mg.
– The other ingredients are: lactose monohydrate, maize starch, copovidone, talc and magnesium stearate.
– The film-coating contains: hypromellose, triacetin and talc.

What Activelle looks like and contents of the pack
The film-coated tablets are white, round 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 sizes:
- 1 x 28 film-coated tablets in a calendar pack
- 3 x 28 film-coated tablets in calendar packs

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:
Member States of the EEA: Activelle – except for United Kingdom (Northern Ireland): Kliovance.

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Other sources of information
Detailed information on this medicine is available on the website of: HPRA