

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you start taking this medicine

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Kliovance is and what it is used for
2. Before you take Kliovance
3. How to use Kliovance
4. Possible side effects
5. How to store Kliovance
6. Further information

1. WHAT KLIOVANCE IS AND WHAT IT IS USED FOR

Kliovance is a continuous combined Hormone Replacement Therapy (HRT). It contains the hormones estradiol and norethisterone acetate. Kliovance is suitable for postmenopausal women with at least 1 year since their last natural period.

The tablets contain 2 hormones: estradiol 1 mg (an oestrogen identical to the one made in the ovaries) and norethisterone acetate 0.5 mg (a progestagen that acts in a similar way to the body's own hormone progesterone).

Kliovance is indicated

- To relieve unpleasant symptoms like hot flushes, night sweats and vaginal dryness, which occur when the oestrogen levels decline and the periods stop (menopause).
- For prevention of osteoporosis (thinning of the bones) in postmenopausal women if they are at high risk of future fractures and if they are unable to take other medications for this purpose.

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

The experience of treating women older than 65 years is limited.

2. BEFORE YOU TAKE KLIOVANCE

Medical check-ups

Before you start taking Kliovance, your doctor will inform you about the risks and benefits of the treatment (see also section 4 Other side effects of combined HRT). Before you start treatment and regularly during treatment, your doctor will evaluate whether Kliovance is the right treatment for you. Your doctor will perform a physical examination. This includes an examination of your breasts, and may include an examination of your abdomen or an internal examination. Your doctor will tell you how often you should go for periodic check-ups, taking into account your general state of health. If you have any close relatives (mother, sister, maternal or paternal grandmother), who has suffered from serious illness, e.g. blood clot or breast cancer, you might be at an increased risk of developing the illness. You should therefore always tell

your doctor about any close relatives suffering from a serious illness, and you should also tell your doctor about any changes, you might find in your breasts.

Once you have started on Kliovance, you should see your doctor for regular check-ups (at least once a year). At these check-ups, your doctor may discuss the benefits and risks of continuing with Kliovance.

As well as regular check-ups with your doctor, be sure to:

- Regularly **check your breasts** for any changes, such as dimpling or sinking of the skin, changes in the nipple, or any lumps you can see or feel.
- Go for regular **breast screening** (mammography) and **cervical smear** tests.

Do not take Kliovance

If any of the following applies to you, **talk to your doctor**. Do not start taking Kliovance:

- If you have or have had **breast cancer**, or if it is suspected.
- If you have or have had **cancer of the womb lining** (endometrium), or if an oestrogen dependent cancer is suspected.
- If you have abnormal **vaginal bleeding**, which has not been diagnosed by your doctor.
- If you have **endometrial hyperplasia** (excessive thickening of the womb lining) that is not being treated.
- If you have or have had **blood clots in a vein** (venous thromboembolism), **in the legs** (deep venous thrombosis) **or the lungs** (pulmonary embolism).
- If you have a **blood clotting disorder** (thrombophilic disorder, such as protein C, protein S, or antithrombin deficiency).
- If you have or have had a **heart attack, stroke, or have angina**.
- If you have or have had **liver problems** 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 other ingredients in Kliovance (listed in section 6 Further information).

Take special care with Kliovance

If you have (or have had) any of the following conditions, **tell your doctor**. He or she may want to see you more often for check-ups. These conditions may in rare cases come back or get worse during treatment with Kliovance:

- If you have any **condition affecting the womb lining**, including fibroids, endometriosis or have had endometrial hyperplasia (excessive thickening of the lining of the womb).
- If you have **a history of blood clots** (thrombosis) or have risk factors for developing blood clots (see Blood clots in a vein) (these risk factors and symptoms for a blood clot are listed in section 4 Other side effects of combined HRT).
- If **any of your immediate family has had breast cancer**, or other cancers related to oestrogen (endometrial cancer).
- If you have **high blood pressure**.
- If you have **a liver disorder** such as liver adenoma (a benign tumour).
- If you have **cardiac or kidney problems**.
- If you have **diabetes or gallstones**.
- If you have **epilepsy or asthma**.
- If you get **migraines or severe headaches**.
- If you have **systemic lupus erythematosus (SLE)** - an autoimmune disease.
- If you have **high levels of fat** in the blood (hypertriglyceridaemia).
- If you have **otosclerosis** (hearing loss)
- If you have **lactose intolerance**.

If you **need a blood test**, tell your doctor that you are taking Kliovance since oestrogen can affect the results of certain laboratory tests.

If you are going to have surgery, talk to your doctor. You may need to stop taking these tablets 4 to 6 weeks before the operation to reduce the risk of a blood clot. Your doctor will tell you when you can start again.

Stop taking Kliovance

If you are experiencing any of the following conditions below, stop taking Kliovance and contact your doctor immediately:

- If you get a **migraine-type headache** for the first time.
- If you develop **yellow skin or eyes** (jaundice) or other liver problems.
- If your **blood pressure goes up** significantly while you are taking Kliovance (symptoms of high blood pressure e.g. headache, tiredness and dizziness).
- If you get **signs of a blood clot** (painful swelling and redness of the legs, sudden chest pain, difficulty in breathing).
- If you **become pregnant**.
- If **any of the conditions** listed in section 2 Do not take Kliovance occur.

Kliovance and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

In women with an intact womb taking oestrogen-only HRT over a long period of time, the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer) is increased.

Taking a progestagen in addition to the oestrogen, as in Kliovance, protects you from this extra risk.

Compare

In women who still have a womb and who are not taking HRT, on average 5 in 1,000 will be diagnosed with endometrial cancer.

For women who still have a womb and take oestrogen-only HRT, the number of extra cases could vary between 5 and 55 in 1,000 users between the ages of 50 and 65 depending on the dose and for how long it is taken.

The addition of a progestagen to oestrogen-only HRT substantially reduces the risk of endometrial cancer.

Breast cancer

Evidence suggests that taking combined oestrogen-progestagen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk is visible after about 3 years. However, it returns to normal within a few years (at most 5) after stopping treatment.

Compare

Women aged 50 to 65 who are not taking HRT, on average 9 to 12 in 1,000 will be diagnosed with breast cancer over a 5-year period.

For women aged 50 to 65 who are taking oestrogen-progestagen HRT over 5 years, the number of extra cases will be 6 in 1,000 users. Looking at women aged 50 to 79 who are not taking HRT, on average 14 in 1,000 will be diagnosed with breast cancer over a 5-year period.

For women aged 50 to 79 who are taking oestrogen-progestagen HRT over 5 years, the number of extra cases will be 4 in 1,000 users.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years. Some studies suggest that the long-term use of combined HRT may carry a similar or slightly smaller risk.

For women who have been taking HRT for over 5 years, there will be 1 extra case per 2,500 users.

Effect of Kliovance 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 HRT users than in non-users, especially during the first year of taking it.

Blood clots are not always serious, but if one travels to the lungs, it can cause chest pain, breathlessness, collapse or even death.

You are generally more likely to get a blood clot in your veins if one or more of the following applies to you. Inform your doctor if any of these situations applies to you:

- You are older
- You are pregnant or have recently had a baby
- You use oestrogen containing preparations
- You or any of your close relatives have ever had a blood clot in the leg, lung or another organ
- You are seriously overweight
- You have systemic lupus erythematosus (SLE)
- You have a blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots (anticoagulant)
- You are unable to walk or stand for a long time because of major surgery, injury or illness (prolonged immobilisation)
- You have cancer

Compare

Women in their 50s who are not taking HRT, on average over a 5-year period, 4 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, the number of extra cases will be 5 in 1,000 users.

Heart disease (heart attack)

There is no evidence that HRT will help to 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 risk of stroke strongly depends on age. Therefore, the number of extra cases of stroke due to use of HRT will rise with more advanced age.

Compare

For women in their 50s who are taking HRT, the number of extra cases will be 3 in 1,000 users over 5 years.

Other conditions

HRT will not prevent memory loss. The risk of probable memory loss may be somewhat higher in women who start using any kind of HRT after the age of 65.

Using other medicines

Some medicines may reduce the effects of Kliovance:

- Drugs used for **epilepsy** (such as phenobarbital, phenytoin and carbamazepine)
- Drugs used for **tuberculosis** (such as rifampicin, rifabutin)
- Drugs used for **HIV infections** (such as nevirapine, efavirenz, ritonavir and nelfinavir)
- Herbal products with **St John's Wort** (*Hypericum perforatum*)

Other medicines may increase the effects of Klioavance:

- Drugs containing **ketoconazole** (a fungicide)

Concomitant administration of **cyclosporine** may cause increased blood levels of 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.

Taking Klioavance with food and drink

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

Pregnancy and breast-feeding

Pregnancy: You should not take Klioavance if you are pregnant.

If you become pregnant stop taking Klioavance immediately and contact your doctor.

Breast-feeding: You should not use Klioavance if you are breast-feeding.

Driving and using machines

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

Important information about some of the ingredients of Klioavance

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

3. HOW TO USE KLIOAVANCE

Always take Klioavance 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. Take the tablet with a glass of water.

Take a tablet every day without stopping. After you have used all 28 tablets in a calendar pack, go straight to using the next pack.

See USER INSTRUCTIONS at the end of the package leaflet

You may **start treatment with Klioavance** 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 for the shortest time that gives you relief from your symptoms. Talk to your doctor if your symptoms are not better after 3 months.

If you take more Klioavance than you should

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

If you forget to take Kliovance

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. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting if you still have your womb.

If you stop taking Kliovance

If you would like to stop taking Kliovance, talk to your doctor first. He/she will explain the effects of stopping treatment and discuss other possibilities with you.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Kliovance can have side effects, although not everybody gets them.

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 Kliovance and seek immediate medical help.**

Bleeding with Kliovance

Kliovance will not cause regular monthly bleeding. When first starting the tablets, some women experience slight vaginal bleeding or spotting.

If you get breakthrough bleeding or spotting, it is usually nothing to worry about, especially during the first few months of taking HRT.

However, contact your doctor as soon as possible:

- If bleeding carries on for more than the first 3 months.
- If bleeding only starts after taking HRT for a while.
- If bleeding continues after stopping HRT.

Your doctor may ask you about any vaginal bleeding with Kliovance at your regular check-ups. You may find it helpful to make a note of any bleeding in your diary.

The frequency of possible side effects listed below is defined using the following convention:

Very common (affects more than 1 user in 10)

Common (affects 1 to 10 users in 100)

Uncommon (affects 1 to 10 users in 1,000)

Rare (affects 1 to 10 users in 10,000)

Very rare (affects less than 1 user in 10,000)

Not known (frequency cannot be estimated from the available data)

Very common side effects

- Breast pain or breast tenderness
- Vaginal bleeding

Common side effects

- 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

- 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

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

Very rare side effects

- 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

Women using HRT have a slightly increased risk of developing the following diseases:

- Breast cancer
- Excessive thickening 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
- Skin and subcutaneous disorders:

- Darkening of the skin (chloasma)
 - Severe condition of the skin that may affect the mouth and other parts of the body (erythema multiforme)
 - Red-purple swellings on the shins, thighs and, less commonly, the arms. Joint and muscle pains and fever may also occur (erythema nodosum)
 - Purple or red-brown spots visible through the skin (vascular purpura)
 - Probable memory loss if HRT is started over the age of 65.
- For more information about these side effects, see section 2.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE KLIOVANCE

Keep out of the reach and sight of children.

Do not use Kliovance 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 from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Kliovance contains

The active substances are estradiol 1 mg (as estradiol hemihydrate) and norethisterone acetate 0.5 mg.

Other ingredients are: lactose monohydrate, maize starch, copovidone, talc and magnesium stearate.
The film-coating contains: hypromellose, triacetin and talc.

What Kliovance looks like and contents of the pack

The film-coated tablets are white, round with a diameter of 6 mm. The tablets are imprinted NOVO 288 on one side and the Novo Nordisk logo (an APIS bull) on the other side.

Pack sizes available:

- 28 film-coated tablets
- 3 x 28 film-coated tablets

Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Novo Nordisk Limited,
Broadfield Park,
Brighton Road,
Crawley,
West Sussex, RH11 9RT

Manufacturer

Novo Nordisk A/S
Novo Allé
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Denmark

This medicinal product is authorised in the Member States of the EEA under the following names:
Member States of the EEA: Activelle – except for United Kingdom: Kliovance.

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USER INSTRUCTIONS

How to use the calendar pack

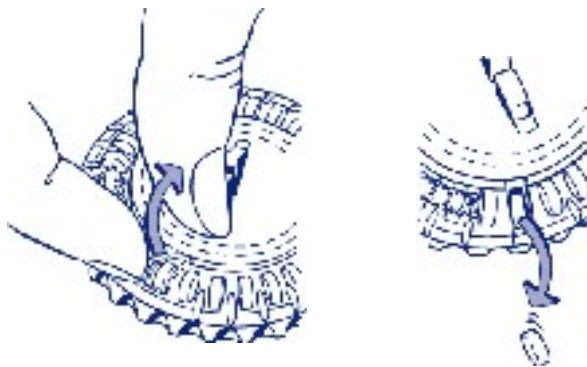
1. Set the day reminder

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



2. 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 once a day.

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

