

Package leaflet: Information for the user

Novofem film-coated tablets estradiol/norethisterone acetate

Read this entire 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 Novofem is and what it is used for
2. What you need to know before you take Novofem
3. How to take Novofem
4. Possible side effects
5. How to store Novofem
6. Contents of the pack and other information

1. What Novofem is and what it is used for

Novofem is a sequential combined Hormone Replacement Therapy (HRT) which is taken every day without interruption. Novofem is used in postmenopausal women with at least 6 months since their last natural period.

Novofem contains 2 hormones, an oestrogen (estradiol) and a progestagen (norethisterone acetate). The estradiol in Novofem is identical to the estradiol produced in the ovaries of women, and is classified as a natural oestrogen. Norethisterone acetate is a synthetic progestagen, which acts in a similar manner as progesterone, another important female sex hormone.

Novofem is used for:

Relief of symptoms occurring after menopause

During the menopause, the amount of the oestrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ('hot flushes'). Novofem alleviates these symptoms after menopause. You will only be prescribed Novofem 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 Novofem to prevent osteoporosis after menopause.

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

2. What you need to know before you take Novofem

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 Novofem, 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 Novofem.

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

Do not take Novofem

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 Novofem.

Do not take Novofem:

- If you have, have had or suspect having **breast cancer**.
- If you have, have had or suspect having **cancer of the womb lining** (endometrial cancer), or any other oestrogen-dependent cancer.
- 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** (venous thromboembolism), 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 are **allergic** (hypersensitive) to **estradiol, norethisterone acetate** or any of the other ingredients of Novofem (listed in section 6 'Contents of the pack and other information').
- If 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 taking Novofem, 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 Novofem. If so, you should see your doctor more often for check-ups:

- fibroids inside your womb
- growth of 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 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
- 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.

Stop taking Novofem 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 Novofem' 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 and 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 (venous thromboembolism)'.

Note: Novofem 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 Novofem 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 between the ages of 50 and 65.

For women aged 50 to 65 who still have a womb and who take oestrogen-only HRT, between 10 and 60 women in 1 000 will be diagnosed with endometrial cancer (i.e. between 5 and 55 extra cases), depending on the dose and for how long it is taken.

Unexpected bleeding

You will have a bleed once a month (so-called withdrawal bleed) while taking Novofem. But, if you have unexpected bleeding or drops of blood (spotting) besides your monthly bleeding, which:

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

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 (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 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/m²)
- 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 Novofem 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 Novofem. 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 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*).

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 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. Novofem contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Novofem with this HCV combination regimen.

Other medicines may increase the effects of Novofem:

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

Novofem 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. Your doctor will advise you.

Laboratory tests

If you need a blood test, tell your doctor or the laboratory staff that you are taking Novofem, because this medicine can affect the results of some tests.

Taking Novofem with food and drink

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

Pregnancy and breast-feeding

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

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

Driving and using machines

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

Important information about some of the ingredients in Novofem

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

3. How to take Novofem

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

If you are not switching from another hormone replacement therapy you can start treatment with Novofem on any convenient day. If you are switching from another hormone replacement therapy ask your doctor when you should start treatment with Novofem.

Take one tablet once a day, at about the same time each day.

Each pack contains 28 tablets

Days 1 – 16 **Take one red** tablet every day for 16 days

Days 17 – 28 **Take one white** tablet every day for 12 days

Take the tablets with a glass of water.

Once you have finished the pack, start a new pack continuing the treatment without interruption. A menstruation-like bleeding (period) usually occurs at the beginning of a new pack.

For further information on the use of the calendar pack, see 'USER INSTRUCTIONS' at the end of the package leaflet.

Your doctor will 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.

Talk to your doctor if you do not experience symptom relief after 3 months of treatment. You should only continue treatment as long as the benefit outweighs the risk.

If you take more Novofem than you should

If you have taken more Novofem than you should, talk to a doctor or pharmacist. An overdose of oestrogens may cause breast tenderness, nausea, vomiting and/or irregular vaginal bleeding (metrorrhagia). Overdosage of progestagens may lead to depressive mood, fatigue, acne and growth of body or facial hair (hirsutism).

If you forget to take Novofem

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 stop taking Novofem

If you would like to stop taking Novofem, 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 Novofem. You may need to stop taking Novofem about 4 to 6 weeks before the operation 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 Novofem 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 Novofem'.

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 heartbeat), feeling dizzy, sweating, which could be signs of anaphylactic reaction/shock. If one of the mentioned symptoms appears, **stop taking Novofem and seek immediate medical help.**

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

- Headache
- Breast tenderness.

Common side effects (may affect up to 1 in 10 people)

- Increased blood pressure, aggravated hypertension
- Vaginal infection with a fungus (e.g. thrush)
- Dizziness, sleeplessness, depression
- Dyspepsia (indigestion), abdominal pain, flatulence
- Nausea (feeling sick)
- Rash, itching
- Vaginal bleeding (see section 2 subsection ‘Unexpected bleeding’)
- Aggravation of uterine fibroids (benign tumour of the womb)
- Oedema (swelling of hands, ankles and feet)
- Weight increase.

Uncommon side effects (may affect up to 1 in 100 people)

- Migraine
- Changes in libido (changes in sexual desire)
- Peripheral embolism and thrombosis (blood clot)
- Vomiting (being sick)
- Gall bladder disease or gallstones
- Hair loss (alopecia)
- Muscle cramps.

Rare side effects (may affect up to 1 in 1 000 people)

- Allergic reactions
- Nervousness
- Vertigo (dizziness)
- Diarrhoea
- Bloating
- Acne
- Uterine fibroid (benign tumour of the womb).

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

- Endometrial hyperplasia (excessive growth of the lining of the womb)
- Increased body and facial hair
- Anxiety
- Visual disturbances
- Seborrhoea
- Vaginal itching.

Other side effects of combined HRT

The following side effects have been reported with other HRTs:

- Various skin disorders:
 - discolouration 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 discolourations of the skin and/or mucous membranes (vascular purpura)
- Dry eyes
- Tear film composition changes.

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 Novofem

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 Novofem contains

- The active substances are estradiol and norethisterone acetate.
The red film-coated tablets contain: estradiol 1 mg (as estradiol hemihydrate).
The white film-coated tablets contain: estradiol 1 mg (as estradiol hemihydrate) and norethisterone acetate 1 mg.
- The other ingredients are: lactose monohydrate, maize starch, hydroxypropylcellulose, talc and magnesium stearate.
Film-coating (red tablets) contains: hypromellose, talc, titanium dioxide (E171), propylene glycol and red iron oxide (E172).
Film-coating (white tablets) contains: hypromellose, triacetin and talc.

What Novofem looks like and contents of the pack

The film-coated tablets are round with a diameter of 6 mm. The red tablets are engraved with NOVO 282. The white tablets are engraved with NOVO 283.

Each pack of 28 tablets contains 16 red tablets and 12 white tablets.

Pack sizes:

- 1x28 film-coated tablets
- 3x28 film-coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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

Supplied in Ireland by:
Novo Nordisk Limited
1st Floor, Block A
The Crescent Building,
Northwood Business Park,
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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: Novofem – except for

France: Novofemme

Spain: Duofemme

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Other sources of information

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

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USER INSTRUCTIONS

How to use the calendar pack

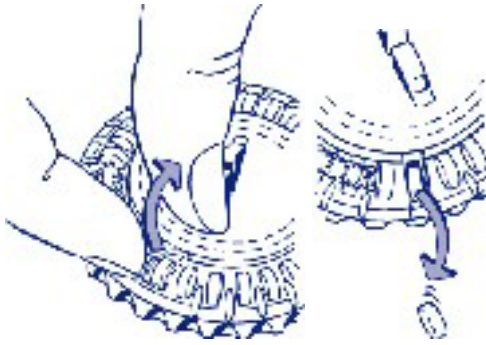
1. Set the day reminder

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.

