Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Novofem®
Film-coated tablets

Active ingredients:

The red tablets contain:
estradiol as hemihydrate 1 mg
The white tablets contain:
estradiol as hemihydrate 1 mg and
norethisterone acetate 1 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?

Novofem is intended for:
- relief of symptoms which are caused by the drop in the level of the hormone estrogen in postmenopausal women whose womb is intact
- prevention of osteoporosis (bone thinning) in postmenopausal women at high risk of future fractures, who cannot be treated with other medicines for this condition.

The experience treating women older than 65 years is limited.

Therapeutic group: sequential estrogen and progestagen products.

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, estrogen (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 estrogen. Norethisterone acetate is a synthetic progestagen, which acts in a manner similar to progesterone, another important female sex hormone.

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 (see section 6 'Additional information').
- you have, have had, or suspect having **breast cancer**.
- you have, have had, or suspect having **cancer of the womb lining**, or any other estrogen dependent 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** (venous thromboembolism) 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 recently 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 results have not returned to normal.
- you have a **rare blood problem called 'porphyria'** which is passed down in families.

If any of the above conditions appears for the first time while taking Novofem, 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 Novofem, you must 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 Novofem.
Go for regular breast screening, as recommended by your doctor.

Before you start treatment with Novofem, tell your doctor if you have ever had any of the following problems, as these problems may return or become worse during treatment with Novofem. 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
- liver disorder, such as a benign tumor
- 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 heart 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.

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 estrogen-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 of 1,000 will be diagnosed with endometrial cancer at age 50 to 65.
For women aged 50 to 65 who still have a womb and who take estrogen-only HRT, between 10 and 60 women in 1,000 will be diagnosed with endometrial cancer (which means 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

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 during 3 years of treatment. After stopping HRT, the additional 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 an extra 0 to 3 cases).
For women aged 50 who start taking combined estrogen-progestagen HRT for 5 years, there will be 21 cases in 1,000 users (this means an extra 4-8 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 an extra 7 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 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
- lumps you can see or feel.

Additionally, you are advised to undergo mammogram screening if 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 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 (this means 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 use.

Blood clots can be serious, and if a blood clot 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 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 under '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 estrogen-progestagen HRT over a 5-year period, 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 those 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 extra cases of stroke due to use of HRT increases 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 (this means 3 extra cases).

Other conditions

HRT does 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. Consult 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 Novofem. If you are unable to stop smoking and you are over 35, consult your doctor.

Tests and follow-up
If you need to have a blood test, tell your doctor or the lab staff that you are taking Novofem, because this medicine can affect the results of certain tests.

Drug interactions
If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist.
Some medicines may interfere with the effect of Novofem, and may cause 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 **human immunodificiency virus (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*)

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 an increase 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. Consult with your doctor.

Other medicines may increase the effect of Novofem:

- medicines containing **ketoconazole** (to treat fungal infections).

Novofem 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
Novofem is for use in postmenopausal women only. If you become pregnant while on this treatment, stop taking Novofem and contact your doctor.
Do 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 this medicine's ingredients
Novofem contains lactose monohydrate. If you have an intolerance to some sugars, contact your doctor before taking Novofem.

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 dosage or about how to take this medicine. Only your doctor will determine your dosage and how you should take this medicine.

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

The recommended dosage is usually:
Take one tablet once a day, at about the same time each day.
Each pack contains 28 tablets
On Days 1 – 16 **Take one red tablet** every day for 16 days
On Days 17 – 28 **Take one white tablet** every day for 12 days

Take (swallow) the tablets with a glass of water.
Do not exceed the recommended dose.

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 symptoms for a period as short as necessary. Talk to your doctor if you think this dose is too strong or not strong enough for you.

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

Novofem is a low-dose tablet for sequential combined treatment so crushing or splitting the tablet cannot be recommended.

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

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 want 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 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 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 Novofem 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

Like with all medicines, using Novofem 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 were 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, 'Before using this medicine'.

Stop taking Novofem and see a doctor immediately
If while you are taking HRT you notice any of the following effects:
- any of the conditions mentioned in section 2 under 'Do not use this medicine if'
- yellowing of the skin or the white of the eye (jaundice); these could be signs of liver disease
- swollen face, tongue and/or throat and/or difficulty swallowing or hives (skin rash), together with difficulty breathing which are suggestive of an angioedema
- significant increase in blood pressure (possible symptoms are headache, fatigue, and 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 breathing.

For additional information see section 2 under 'Blood clots in a vein (venous thromboembolism)'.

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 (skin rash), itching, swelling, difficulty breathing, low blood pressure (pale, cool skin, fast heartbeat), dizziness, sweating, which could be signs of anaphylactic reaction/shock. If you get any of the listed symptoms, **stop taking Novofem and seek immediate medical help**.

Very common side effects (may affect more than 1 in 10 women)
- headache
- breast tenderness

Common side effects (may affect up to 1 in 10 women)
- increased blood pressure, aggravated hypertension
- vaginal infection with a fungus
- dizziness, sleeplessness, depression
- dyspepsia (indigestion), abdominal pain, flatulence
- nausea
- rash, itching
- vaginal bleeding (see section 2 under 'Unexpected bleeding')
- aggravation of uterine fibroids (benign tumor of the womb)
- edema (swelling of hands, ankles and feet)
- weight gain.

Uncommon side effects (may affect up to 1 in 100 women)
- migraine
- changes in sex drive (libido)
- peripheral embolism and thrombosis (blood clot)
- vomiting
- gall bladder disease or gallstones
- hair loss (alopecia)
- muscle cramps.

Rare side effects (may affect up to 1 in 1,000 women)
- allergic reactions
- nervousness
- vertigo (dizziness)
- diarrhea
- bloating
- acne
- uterine fibroid (benign tumor 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
- seborrhea
- vaginal itching.

Additional side effects of combined HRT
The following side effects have been reported with other HRTs:
- 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)
- Dry eyes
- Tear film composition changes.

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 link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also follow 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 a doctor.

Do not use the medicine after the expiry date (exp. date) which is stated on the label and outer carton. The expiry date refers to the last day of that month.

Storage conditions
Store below 25°C. Do not refrigerate.

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

Do not throw away any medicine 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 (white tablet 36.8 mg, red tablet 37.3 mg), maize starch, hydroxypropylcellulose, talc and magnesium stearate

Film coating (red tablets): hypromellose, talc, titanium dioxide (E171), propylene glycol, and red iron oxide (E172).
Film coating (white tablets): hypromellose, triacetin and talc.

What the medicine looks like and contents of the pack:
The film-coated tablets are round and are 6 mm in diameter. 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 size: 28 film-coated tablets.

Registration holder's name and address:
Novo Nordisk Ltd., 1 Atir Yeda St., Kfar-Saba, 4464301.

Manufacturer's name and address:
Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

Revised in January 2024.

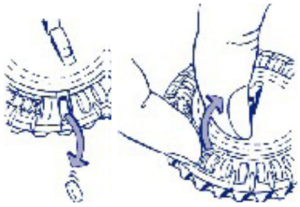
Registration number of the medicine in the Ministry of Health's National Drug Registry: 127-11-30604

User Instructions

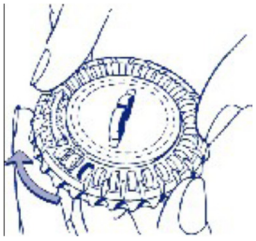
How to use the calendar pack

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



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