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

Estrofem 1 mg
Film-coated tablets

Estrofem 2 mg
Film-coated tablets

Active ingredient:

estradiol as hemihydrate 1 mg

estradiol as hemihydrate 2 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 to treat 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?

- Estrofem is a hormone replacement therapy (HRT) that is used to treat symptoms of estrogen deficiency in postmenopausal women.
- Estrofem is used to prevent osteoporosis (bone thinning) in postmenopausal women who are at high risk of future fractures and who cannot be treated with other medicines for this condition.

Estrofem is used in women who have had their womb removed and therefore do not require combined estrogen-progestagen therapy.
There is only limited experience of treating women older than 65 years with Estrofem.

Therapeutic group: natural and semi-synthetic estrogens.

When a woman's period stops during menopause, the amount of estrogen produced by her body drops. This can cause symptoms such as hot face, neck and chest ('hot flushes'). Estrofem alleviates these symptoms after menopause. Only take Estrofem if your symptoms seriously hinder your daily life.

2. Before using this medicine

Do not use this medicine if:

- you are **sensitive** (allergic) to **estradiol** or to any of the other ingredients in this medicine (listed in section 6 'Additional information')
- you have or have ever had **breast cancer**, or if you are suspected of 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 such a cancer
- you have any **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) 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 appear for the first time while taking Estrofem, stop taking it at once and consult your doctor immediately.

Medical history and regular check-ups

The use of HRT carries risks which need to be considered when deciding whether to start the treatment, or when deciding 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 should 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 Estrofem 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 Estrofem.

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

Special warnings about using this medicine

Before you start treatment with Estrofem, tell your doctor if you have ever had any of the following problems, as these problems may return or become worse during treatment with Estrofem. 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.

Note: Estrofem 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).
Taking a progestagen in addition to the estrogen for at least 12 days of each 28-day cycle protects you from this extra risk. Your doctor will prescribe a progestagen separately if you still have your womb. If you have had your womb removed (a hysterectomy), discuss with your doctor whether you can safely take this product without a progestagen.

Compare
In women who still have a womb and who are not taking HRT, on average, 5 of 1,000 will be diagnosed with cancer of the womb lining 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 Estrofem. But if you have unexpected bleeding or spotting besides your monthly bleeding, which:
- carries on for more than the first 6 months
- starts after you have been taking Estrofem more than 6 months
- carries on after you have stopped taking Estrofem

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 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 estrogen-progestagen HRT for 5 years, there will be 21 cases in 1,000 users (this means an extra 4 to 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 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 reaches 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 applies 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 Estrofem 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).
For women in their 50s who have had their womb removed and have been taking estrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1,000 users (this means 1 extra case).

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.

For women who have had their womb removed and are taking estrogen-only therapy there is no increased risk of developing a heart disease.

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 increased risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

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

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 Estrofem. If you are unable to stop smoking and you are over 35, consult your doctor.

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 Estrofem. 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, rifabutin)
- medicines for **HIV infection** (such as nevirapine, efavirenz, ritonavir and nelfinavir)
- products containing ***Hypericum perforatum*** (St. John's wort)

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

Pregnancy and breastfeeding
Estrofem is for use in postmenopausal women only. If you become pregnant while on this treatment, stop taking Estrofem and contact your doctor.

Driving and using machines
Estrofem has no known effects on the ability to drive or use machines.

Important information about some of this medicine's ingredients
Estrofem contains lactose monohydrate. If you have an intolerance to some sugars, contact your doctor before taking Estrofem.

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 dose and how you should take this medicine.

The recommended dosage is usually:
Take one tablet 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.
If your womb has been removed or if you have no vaginal bleeding and you are not taking other hormone therapy products, you can start treatment on any convenient day.

If you have taken other HRT products until now, ask your doctor or pharmacist when you should start taking Estrofem.
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 dosage to treat your symptoms for as short a period as necessary. Talk to your doctor if you think this dose is too strong or not strong enough for you.

Do not exceed the recommended dose.

If you have had your womb removed, your doctor will not prescribe a progestagen (another female hormone) in addition unless you have had a condition called endometriosis (deposition of uterine tissue outside the womb).
If you get breakthrough bleeding or spotting, it is usually nothing to worry about, especially during the first few months of taking HRT (see also section 2, 'HRT and cancer', 'Excessive thickening of the lining of the womb [endometrial hyperplasia] and cancer of the lining of the womb [endometrial cancer]' for more information).

There is no information about crushing/splitting, so this practice is not recommended.

If you have accidentally taken a higher dose
If you have taken more Estrofem than you should, talk to a doctor or pharmacist. An overdose of Estrofem could cause nausea or vomiting. 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, 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 your 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 want to stop taking Estrofem, 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 Estrofem. You may need to stop taking Estrofem 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 Estrofem 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 Estrofem 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 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
- probable memory loss if HRT is started over the age of 65.

For more information about these side effects, see section 2.

Stop taking Estrofem and see a doctor immediately

If while you are taking HRT you notice any of the following effects:

- any of the conditions listed in section 2 **'Do not use this medicine if:'**
- yellowing of the skin or the white of the eye (jaundice), these could be signs of liver disease
- 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 breathing.

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

Hypersensitivity/allergy (uncommon side effect – affects up to 1 in 100 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, 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 Estrofem and seek immediate medical help.**

Common side effects (affect up to 1 in 10 users)

- depression
- headache
- abdominal (stomach) ache
- nausea
- leg cramps
- breast pain, breast tenderness or breast enlargement
- edema (retention of fluid)
- weight gain.

Uncommon side effects (affect up to 1 in 100 users)

- abnormal vision
- blood clots in the veins (venous embolism)
- heartburn
- vomiting
- flatulence (gas)
- gallstones

- itching or hives (urticaria).

Very rare side effects (affect up to 1 in 10,000 users)

- irregular vaginal bleeding*
- migraine, worse than before
- stroke
- insomnia (being unable to sleep)
- epilepsy
- changes in sex drive
- vaginal infection caused by a fungus
- deterioration of asthma
- dizziness
- diarrhea
- hair loss
- increased blood pressure.

*If prescribed for women with a womb

The following side effects have been reported with other HRTs:

- 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).

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 package. The expiry date refers to the last day of that month.

Storage conditions
Store below 25°C. Do not refrigerate.
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 ingredient, this medicine also contains:

Estrofem 1 mg:
lactose monohydrate (37.3 mg), maize starch, hydroxypropylcellulose, talc, magnesium stearate.

The tablet coating contains:

hypromellose, talc, titanium dioxide (E171), propylene glycol and red iron oxide (E172).

Estrofem 2 mg:
lactose monohydrate (36.8 mg), maize starch, hydroxypropylcellulose, talc, magnesium stearate.

The tablet coating contains:

hypromellose, talc, titanium dioxide (E171), macrogol 400 and indigo carmine (E132).

What the medicine looks like and contents of the pack

Estrofem 1 mg:
Round, red, film-coated tablets measuring 6 mm in diameter. The tablets are embossed on one side with NOVO 282.

Estrofem 2 mg:
Round, blue, film-coated tablets measuring 6 mm in diameter. The tablets are embossed on one side with NOVO 280.

Pack size: 1 x 28 film-coated tablets in a pack.

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.

This leaflet was revised in December 2020.

Registration number of the medicine in the Ministry of Health's National Drug Registry:

Estrofem 1 mg: 117 54 29845

Estrofem 2 mg: 060 75 27769

User Instructions:

How to use the calendar pack

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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 once a day.

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

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