

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Estrofem 2 mg
Film-coated tablets
estradiol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: estradiol 2 mg (as estradiol hemihydrate)

3. LIST OF EXCIPIENTS

Excipients include lactose monohydrate. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

1x28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C
Do not refrigerate

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

PA 218/50/1

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS DISPENSER LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
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Estrofem 2 mg
Film-coated tablets
estradiol 2 mg (as estradiol hemihydrate)

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

28 film-coated tablets

6. OTHER

7. MANUFACTURER / MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

PA 218/50/1

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
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Estrofem
2 mg film-coated tablets
estradiol hemihydrate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

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

What is in this leaflet

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

1. What Estrofem is and what it is used for

Estrofem is a Hormone Replacement Therapy (HRT). It contains the female hormone estradiol. Estrofem is used in postmenopausal women, particularly in women who have had their womb removed (have had a hysterectomy) and therefore do not require combined oestrogen/progestagen therapy.

Estrofem is used for:

Relief of symptoms occurring after menopause

During the menopause, the amount of oestrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ('hot flushes'). Estrofem alleviates these symptoms after menopause. You should only be prescribed Estrofem if your symptoms seriously hinder your daily life.

Prevention of osteoporosis (thinning of the bones) if you are at high risk of future fracture and if you are unable to take other medications for this purpose.

There is only limited experience of treating women older than 65 years with Estrofem.

2. What you need to know before you take Estrofem

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 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 on 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 with Estrofem.

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

Do not take Estrofem

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 Estrofem.

Do not take Estrofem:

- If you have or have ever had **breast cancer**, or if you are suspected of having it.
- If you have or have had **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it.
- If you have any **unexplained vaginal bleeding**.
- If you have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated.
- If you have or have ever had a **blood clot in a vein** (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism).
- If you have a **blood clotting disorder** (such as protein C, protein S or antithrombin deficiency).
- If you have or recently have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke or angina**.
- If you have or have ever had a **liver disease** and your liver function tests have not returned to normal.
- If you have a **rare blood problem called 'porphyria'** which is passed down in families (inherited).
- If you are **allergic** (hypersensitive) to **estradiol** or any of the other ingredients of Estrofem (listed in section 6, 'Contents of the pack and other information').

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

Warnings and precautions

Talk to your doctor before taking Estrofem. 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 Estrofem. 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 (thrombosis)')
- 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
- hereditary and acquired angioedema.

Stop taking Estrofem 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 Estrofem' section
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease
- swollen face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing which are suggestive of an angioedema
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness)
- migraine-like headaches which happen for the first time
- if you become pregnant
- if you notice signs of a blood clot, such as:
 - painful swelling and redness of the legs
 - sudden chest pain
 - difficulty in breathing.

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

Note: Estrofem is not a contraceptive. If it has been 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).

Taking a progestagen in addition to the oestrogen for at least 12 days of each 28-day cycle protects you from this extra risk. So 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 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 Estrofem. 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 Estrofem more than 6 months
 - carries on after you have stopped taking Estrofem
- see your doctor as soon as possible.

Breast cancer

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

Compare

Women aged 50 to 54 who are not taking HRT, on average, 13 to 17 in 1 000 will be diagnosed with breast cancer over a 5-year period.

For women aged 50 who start taking oestrogen-only HRT for 5 years, there will be 16-17 cases in 1 000 users (i.e. an extra 0 to 3 cases).

For women aged 50 who start taking oestrogen-progestagen HRT for 5 years, there will be 21 cases in 1 000 users (i.e. an extra 4 to 8 cases).

Women aged 50 to 59 who are not taking HRT, on average, 27 in 1 000 will be diagnosed with breast cancer over a 10-year period.

For women aged 50 who start taking oestrogen-only HRT for 10 years, there will be 34 cases in 1 000 users (i.e. an extra 7 cases).

For women aged 50 who start taking oestrogen-progestagen HRT for 10 years, there will be 48 cases in 1 000 users (i.e. an extra 21 cases).

Regularly check your breasts. See your doctor if you notice any changes such as:

- dimpling of the skin
- changes in the nipple
- any lumps you can see or feel.

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

Ovarian cancer

Ovarian cancer is rare - much rarer than breast cancer. The use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer.

The risk of ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2 000 users (i.e. about 1 extra case).

Effect of HRT on heart and circulation

Blood clots in a vein (thrombosis)

The risk of **blood clots in the veins** is about 1.3 to 3 times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

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

- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, 'If you need to have surgery')
- you are seriously overweight (BMI > 30 kg/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 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 oestrogen-progestagen HRT for over 5 years, there will be 9 to 12 cases in 1 000 users (i.e. an extra 5 cases).

For women in their 50s who have had their womb removed and have been taking oestrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1 000 users (i.e. 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 oestrogen-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 oestrogen-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 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.

Other medicines and Estrofem

Some medicines may interfere with the effects 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)
- 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 CHCs containing ethinylestradiol. Estrofem contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Estrofem with this HCV combination regimen.

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.

Estrofem with food and drink

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

Pregnancy and breast-feeding

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

Driving and using machines

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

Estrofem contains lactose monohydrate

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Estrofem contains sodium

Estrofem contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

Laboratory tests

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

3. How to take Estrofem

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

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.

Take one tablet every day, at about the same time each day. Once you have finished all the 28 tablets in the pack, start a new pack continuing the treatment without interruption.

For instructions 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 as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

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 have taken other HRT products until now, ask your doctor or pharmacist when you should start taking Estrofem.

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).

If you take more Estrofem than you should

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

If you forget to take Estrofem

If you forget to take your tablet at the usual time, take it within the next 12 hours. If more than 12 hours have gone by, skip the missed dose and start again as normal the next day. Do not take a double dose to make up for a forgotten tablet. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting if you still have your womb.

If you stop taking Estrofem

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 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 Estrofem. You may need to stop taking Estrofem about 4 to 6 weeks before the operation to reduce the risk of a blood clot (see section 2, 'Blood clots in a vein'). Ask your doctor when you can start taking Estrofem again.

4. Possible side effects

Like all medicines, this medicine can cause 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 Estrofem'.

Hypersensitivity/allergy (uncommon side effect – may affect up to 1 in 100 people)

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 Estrofem and seek immediate medical help.**

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

- Depression
- Headache
- Abdominal (stomach) pain
- Feeling sick (nausea)
- Leg cramps
- Breast pain, breast tenderness or breast enlargement
- Irregular vaginal bleeding*
- Oedema (retention of fluid)
- Weight increase or weight decrease.

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

- Dizziness
- Palpitations
- Abnormal vision
- Blood clots in the veins (venous embolism)
- Heartburn (dyspepsia)
- Vomiting
- Flatulence or bloating
- Gallstones
- Itching or hives (urticaria).

Very rare side effects (may affect up to 1 in 10 000 people)

- Migraine, worse than before
- Stroke
- Insomnia (being unable to sleep)
- Epilepsy
- Changes in libido
- Vaginal infection caused by a fungus
- Deterioration of asthma
- Anxiety
- Fatigue
- Contact lens intolerance
- Acne
- Premenstrual-like syndrome
- Diarrhoea
- Hair loss (alopecia)
- Increased blood pressure.

*If prescribed for women with a uterus

The following side effects have been reported with other HRT's:

- 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).

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 Estrofem

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 carton after 'EXP'. The expiry date refers to the last day of that month.

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. Contents of the pack and other information

What Estrofem contains

- The active substance is estradiol (as estradiol hemihydrate).
- Each film-coated tablet contains estradiol 2 mg (as estradiol hemihydrate).
- The other ingredients are: lactose monohydrate, maize starch, hydroxypropylcellulose, talc and magnesium stearate.
- The film-coating contains: hypromellose, talc, titanium dioxide (E171), macrogol 400, indigo carmine (E132).

What Estrofem looks like and contents of the pack

The film-coated tablets are blue, round with a diameter of 6 mm. The tablets are imprinted NOVO 280 on one side.

Pack size available:

1x28 film-coated tablets

Marketing Authorisation Holder and Manufacturer

Novo Nordisk A/S

Novo Allé

DK-2880 Bagsværd, Denmark

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the web site of: HPRA

Estrofem is a registered trademark owned by Novo Nordisk Health Care AG, Switzerland.

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USER INSTRUCTIONS

How to use the calendar pack



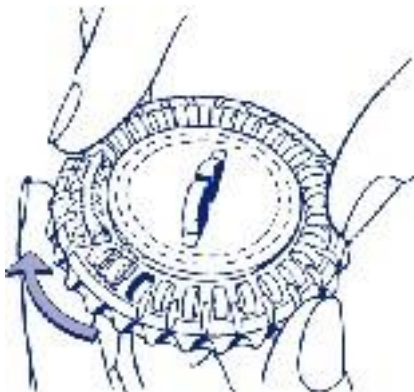
1. Set the day reminder

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.