PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

Estrofem® 1 mg film-coated tablets

Estrofem® 2 mg film-coated tablets

Estradiol

Contains sugar:

Estrofem® 1 mg: Each tablet contains 37,3 mg lactose monohydrate.

Estrofem®: Each tablet contains 36,8 mg lactose monohydrate.

Read all of this leaflet carefully before you start using Estrofem®

Keep this leaflet. You may need to read it again.

If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.

Estrofem® has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What Estrofem® is and what it is used for

Estrofem® is a hormone replacement therapy (HRT) that is used:

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

Estrofem® is prescribed for women who have had their womb removed (have had a hysterectomy).

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

2. What you need to know before you take Estrofem®

Do not take Estrofem®:

If any of the following applies to you, do not take Estrofem®:

- If you are allergic (hypersensitive) to estradiol or any other ingredients in Estrofem® (see section 6).
- If you have, have had or suspect you have breast cancer.
- If you have a family history of breast cancer.
- If you have or suspect you have or have had a hormone dependent tumour (e.g. cancer of the lining of the womb).
- If you have any vaginal bleeding, which has not been diagnosed by your doctor.
- If you have endometrial hyperplasia (excessive growth of the womb lining) that is not being treated.
- If you have a blood clot (like deep vein thrombosis (DVT) or lung embolism) or previously have had a blood clot without obvious cause e.g. in connection with surgery or pregnancy (see section “Blood clots”).
- Have a blood clotting disorder (such as protein C, protein S or antithrombin deficiency).
- Have or previously have had a disease caused by blood clots in the arteries, such as a heart attack or angina.
- If you have high blood pressure.
- If you have or have had a liver disorder and your liver tests have not returned to normal.

- If you have porphyria (a liver enzyme disease).
- If you are pregnant.
- If you are known to have inherited genetic changes called BRCA1 and/or BRCA2 genes.
- If you started your menstrual periods early (before the age of 12 years).
- If you have a history of non-cancerous breast diseases such as atypical hyperplasia or lobular carcinoma *in situ*.
- If you had any previous treatment using radiation therapy to the chest or breast.
- If you have been treated or exposed while in your mother's womb to a medicine called diethylstilbestrol (DES).

Warnings and precautions

Take special care with Estrofem®:

If you have (or have had) any of the following conditions, tell your doctor. Your doctor may then want to follow your treatment up more closely. Rarely, these conditions may come back or get worse during treatment with Estrofem®:

- If you have any condition affecting the womb lining, such as a leiomyoma (benign tissue tumour), endometriosis (presence of womb lining tissue outside the womb) or have had endometrial hyperplasia (excessive growth of the womb lining).
- If you have a history of blood clots (thrombosis) or have risk factors for blood clots (these risk factors and symptoms for a blood clot are listed in section “Blood clots”).
- If any of your immediate family has had cancers related to estrogen (endometrial cancer).
- If you have a liver disorder such as liver adenoma (a benign tumour).
- If you have a kidney or heart disorder.
- If you have diabetes or gallstones.
- If you have epilepsy (fits) or asthma.
- If you have migraine or severe headache.
- If you have systemic lupus erythematosus (SLE, autoimmune collagen disease, which may affect many organ systems).

- If you have high levels of fat in your blood (hypertriglyceridemia).
- If you have otosclerosis (hearing loss sometimes linked to pregnancy).
- You are on treatment for depression.
- You have had depression with previous use of estrogen and/or progesterone/progestogen-containing medicines.
- You have a substance abuse problem.
- You have an underlying psychiatric disorder such as post-traumatic stress disorder or bipolar disorder.
- You have a family history of mental disorders.
- You have a history of physical or sexual abuse.

Estrogen containing medicines, including Estrofem®, may cause mood changes and depression, which may be severe. Severe depression is associated with a higher risk of suicidal thoughts/behaviour (e.g. talking about suicide, withdrawing from social contact, having mood swings, being preoccupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Contact your doctor in case of mood changes and depressive symptoms, including shortly after beginning treatment of Estrofem®.

If you need a blood test, tell your doctor that you are taking Estrofem®, since estrogen can affect the results of certain laboratory tests.

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

Stop taking Estrofem®

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

- If you get a migraine-type headache for the first time.
- If you develop yellow skin or eyes (jaundice) or other liver problems.
- If you have symptoms of significant increase in blood pressure (e.g. headache).
- If you become pregnant.
- If any of the conditions listed contraindications "Do not take Estrofem®" occur.

Medical check-ups

Before you start taking Estrofem®, your doctor should ask about your own and your family's medical history. Your doctor may decide to examine your breasts and/or your abdomen, and may do an internal examination - but only if these examinations are necessary for you, or if you have any special concerns.

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

Be sure to:

- Go for regular breast screening and cervical smear tests.
- Regularly check your breasts for any changes such as dimpling of the skin, changes in the nipple, or 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/health care provider who is actually taking the x-ray that you use Estrofem®, as this medicine 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.

Safety of HRT

As well as benefits, Estrofem® has some risks which you need to consider when you're deciding whether to take it or whether to carry on taking it.

Effects on your heart or circulation

Heart disease

Estrofem® is not recommended for women who have heart disease or have had heart disease recently. If you have ever had heart disease, talk to your doctor to see if you should be taking Estrofem®.

Estrofem® will not help to prevent heart disease.

Studies with one type of HRT (containing conjugated estrogen plus the progestagen, medroxyprogesterone acetate (MPA) have shown that women may be more likely to get heart disease during the first year of taking the medicine.

Stroke

Recent research suggests that HRT such as Estrofem® increases the risk of having a stroke.

If you have had a stroke in the past, talk to your doctor.

If you get unexplained migraine-type headaches, with or without disturbed vision, see a doctor as soon as possible and do not take any more Estrofem® until your doctor says you can. These headaches may be an early warning sign of a stroke.

Blood clots

Estrofem® may increase the risk of blood clots in the veins (also called deep vein thrombosis, or DVT), especially during the first year of taking it.

If a blood clot travels to the lungs, it can cause chest pain, breathlessness, collapse or death. This condition is called pulmonary embolism, or PE.

Effects on your risk of developing cancer

Estrofem® and breast cancer

Women who have breast cancer, or have had breast cancer in the past, should not take Estrofem®.

Evidence shows that taking combined estrogen-progestagen or estrogen-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 79 who are not taking HRT, on average, 9 to 17 in 1 000 will be diagnosed with breast cancer over a 5-year period. For women aged 50 to 79 who are taking estrogen-progestagen HRT over 5 years, there will be 13 to 23 cases in 1 000 users (i.e. an extra 4 to 6 cases).

Breast cancer has been diagnosed slightly more often in women who use HRT than in women of the same age who do not use HRT. This slight increase in the number of breast cancer diagnoses gradually disappears during the course of the 10 years after stopping use of HRT. When you are using Estrofem®, you must perform monthly breast self-examinations. Your doctor will advise you on when to report for breast examinations and any appropriate investigations.

Your risk of breast cancer is also higher:

- If you have a close relative (mother, sister or grandmother) who has had breast cancer.
- If you are seriously overweight.

If you notice any changes in your breast, such as:

- Dimpling of the skin
- Changes in the nipple
- Any lumps you can see or feel, make an appointment to see your doctor as soon as possible.

Endometrial cancer (cancer of the lining of the womb)

Taking Estrofem® for a long time can increase the risk of cancer of the lining of the womb (the endometrium). Taking a progestagen as well as the estrogen helps to lower the extra risk.
If you get breakthrough bleeding or spotting, it's usually nothing to worry about, especially during the first few months of taking Estrofem®.

But if the bleeding or spotting:

- Carries on for more than the first few months,
- Starts after you've been on Estrofem® for a while,
- Carries on even after you have stopped taking Estrofem®, make an appointment to see your doctor.

Ovarian cancer

Some studies have indicated that taking estrogen-only HRT such as Estrofem® for more than 5 years may increase the risk of ovarian cancer.

Other medicines and Estrofem®

Always tell your health care if you are taking any other medicine. (This includes all complementary or traditional medicines).
Some medicines interfere with the effects of Estrofem® and might led to irregular bleeding:

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

Estrofem® 1 mg/2 mg may reduce the effect of lamotrigine (used for the treatment of seizures) which may reduce seizure control.
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.

Estrofem® with food, drink and alcohol

See section 3.

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before taking Estrofem®.

Do not take Estrofem® if you suspect being pregnant, are pregnant or breastfeeding.

Driving and using machines

Estrofem® has no known effect on the use of any machines or the ability to drive safely.

Estrofem® contains lactose monohydrate

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 Estrofem®.

3. How to take Estrofem®

Do not share medicines prescribed for you with any other person.

Always take Estrofem® exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

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 once a day, at about the same time each day.
- Take the tablet with a glass of water.
- Take a tablet every day without stopping. After you have used all 28 tablets in a calendar pack, go straight to using the next pack.
- Tablets can be taken with or without food and drink.

For instructions on the use of the calendar pack, see “How to use the calendar dial pack" at the end of the package leaflet.

Talk to your doctor if your symptoms are not better after three months of treatment.

If you have taken other HRT products until now, please ask your doctor or pharmacists when you should start taking Estrofem®.

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.

In the event of overdosage, consult your doctor or pharmacist. If neither is available contact the nearest hospital or poison control centre.

If you forget to take a dose of 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.

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 Estrofem® ask your doctor or pharmacist.

4. Possible side effects

Estrofem® can cause side effects.

Not all side effects reported for Estrofem® are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, please consult your doctor, pharmacist or other health care provider for advice.

If any of the following happens, stop taking Estrofem® and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Swelling of your hands, feet, ankles, face, lips, tongue, mouth or throat, which may cause difficulty in swallowing or breathing; low blood pressure (paleness and coldness of skin, rapid heartbeat), feeling dizzy, sweating;
- Rash, hives or itching;
- Fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Estrofem®. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

Less frequent side effects:

- Blood clots in the veins (venous embolism).

Side effects with unknown frequencies:

- Migraine, worse than before,
- Stroke.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

Frequent side effects:

- Depression.
- Headache.
- Abdominal (stomach) pain.
- Feeling sick (nausea).
- Leg cramps.

- Breast pain, breast tenderness or breast enlargement.
- Oedema (retention of fluid).
- Weight increase.

Less frequent side effects:

- Abnormal vision
- Heartburn (dyspepsia)
- Vomiting
- Flatulence or bloating
- Gallstones
- Itching or hives (urticaria).

Side effects with unknown frequencies:

- Irregular vaginal bleeding*.
- Insomnia (being unable to sleep).
- Epilepsy.
- Changes in libido.
- Vaginal infection caused by a fungus.
- Deterioration of asthma.
- Dizziness.
- Diarrhoea.
- Hair loss (alopecia).
- Increased blood pressure.

**If prescribed for women with a uterus.*

Other side effects of Estrofem®:

The below mentioned side effects have been reported after taking estrogen and estrogen/ progestagen products. For further information consult section *Warnings and precautions* above.

- Heart disease.
- Stroke.
- Blot clots.
- Breast cancer.
- Endometrial cancer.
- Ovarian cancer.
- Suicidal thoughts/behaviour and suicide.

Dementia

Estrofem® will not prevent memory loss. In one study of women who started using combined HRT after the age of 65, a small increase in the risk of dementia was observed. It is not known whether these results also applies to women younger than 65 years when starting the treatment or to women taking other HRT preparations.

Gall bladder disease

Gall bladder disease has been reported after treatment with estrogen/progestagen.

Effects on the skin

Brown pigmented patches in the face (chloasma), skin rashes including red inflammation on the hands or the legs (erythema multiforme), formation of tender, red nodules on the front of the legs/knees (erythema nodosum) or a bruise-like rash (vascular purpura) and itching (pruritus).

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist. You can also report side effects to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

By reporting side effects, you can help provide more information on the safety of Estrofem®.

5. How to store Estrofem®

Store all medicines out of reach of children.

Store at or below 25 °C.

Do not refrigerate.

Keep the container in the outer carton until required for use.

Do not use Estrofem® after the expiry date stated on the label of the calendar dial pack and outer carton.

Return all unused medicine to your pharmacist. Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What Estrofem® contains

Estrofem® contains the female sex hormone estradiol. This is identical to the estradiol produced in the ovaries of women, and is classified as a natural estrogen.

Estrofem® 1 mg: Each tablet contains 1 mg estradiol (as estradiol hemihydrate) as the active ingredient.

Estrofem®: Each tablet contains 2 mg estradiol (as estradiol hemihydrate) as the active ingredient.

The other ingredients are hydroxypropylcellulose (E463); hypromellose; lactose monohydrate; magnesium stearate (E572); maize starch; talc (E553b); and titanium dioxide (E171).

Estrofem® 1 mg:

Red iron oxide (E172), propylene glycol (E1520).

Estrofem®:

Indigo carmine (E132), macrogol 400.

What Estrofem® looks like and contents of the pack

Estrofem® 1 mg: Round, red, film-coated, biconvex tablets engraved with NOVO 282. Diameter 6 mm.

Estrofem®: Round, blue, film-coated, biconvex tablets engraved with NOVO 280. Diameter 6 mm.

Estrofem® is supplied in a calendar dial pack each containing 28 tablets.

The calendar dial pack with 28 tablets consists of the following 3 parts:

- The base made of coloured non-transparent polypropylene.
- The ring-shaped lid made of transparent polystyrene.
- The centre-dial made of coloured non-transparent polystyrene.

Holder of certificate of registration

Novo Nordisk (Pty) Ltd

90 Grayston Drive

Sandown

Sandton

Gauteng

2031

011 202 0500

This leaflet was last revised in

Date of registration:

Estrofem® 1 mg: 08 October 2001

Estrofem®: 27 August 1979.

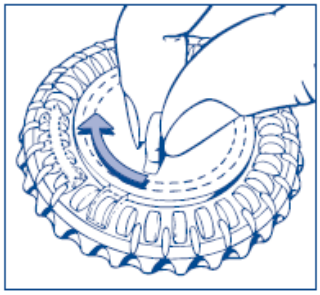
Date of revision: 17 February 2025

Registration numbers

Estrofem® 1 mg: 34/21.8.1/0159

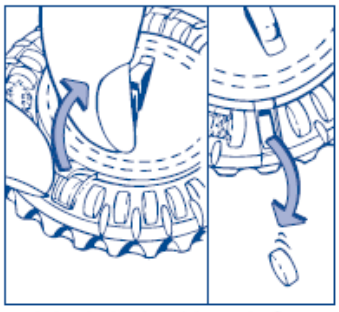
Estrofem®: J/21.8.1/214

Instructions for use of the calendar dial pack



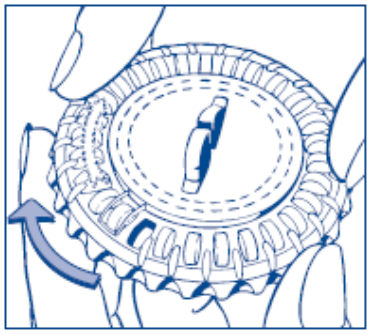
1. Set the day reminder:

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 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.