SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Estrofem 1 mg film-coated tablets
Estrofem 2 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains estradiol 1 mg or 2 mg (as estradiol hemihydrate).

Excipient with known effect: lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Estrofem 1 mg: Red, film-coated, round, biconvex tablets, engraved with NOVO 282.
Diameter 6 mm.

Estrofem 2 mg: Blue, film-coated, round, biconvex tablets, engraved with NOVO 280.
Diameter 6 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women.

Estrofem is particularly for women who have been hysterectomised and therefore do not require combined oestrogen/progestagen therapy.

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Estrofem is an oestrogen-only product for hormonal replacement. Estrofem is administered orally, one tablet daily without interruption. For initiation and continuation of treatment of menopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.

A switch to a higher dose or a lower dose of Estrofem could be indicated if the response after three months is insufficient for satisfactory symptom relief or if the tolerability is not satisfactory.

In women without a uterus, Estrofem may be started on any convenient day. In women with a uterus who present amenorrhoea and are being transferred from a sequential HRT, Estrofem may be initiated on day 5 of bleeding and only in combination with a progestagen for at least 12–14 days; if transferred from a continuous-combined HRT, Estrofem along with a progestin, may be started on any convenient day. The progestagen type and dose should provide sufficient inhibition of the oestrogen induced endometrial proliferation (see also section 4.4).

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next 12 hours. If more than 12 hours have passed, the tablet should be discarded. Forgetting a dose for women with a uterus may increase the likelihood of breakthrough bleeding and spotting.

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestagen in hysterectomised women.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known, past or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disease disorders (e.g. protein C, protein S or antithrombin deficiency (see section 4.4))
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Porphyria.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

As the experience in treating women with a premature menopause (due to ovarian failure or surgery) is limited, the evidence regarding the risks associated with HRT in the treatment of premature menopause is also limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices and modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Estrofem, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension

– Liver disorders (e.g. liver adenoma)
– Diabetes mellitus with or without vascular involvement
– Cholelithiasis
– Migraine or (severe) headache
– Systemic lupus erythematosus
– A history of endometrial hyperplasia (see below)
– Epilepsy
– Asthma
– Otosclerosis.

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

– Jaundice or deterioration in liver function
– Significant increase in blood pressure
– New onset of migraine-type headache
– Pregnancy.

Endometrial hyperplasia and carcinoma

In women with intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2 to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

The addition of a progestagen for at least 12 days per cycle in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

Breakthrough bleeding and spotting may occur during the first months of treatment in women with intact uterus. If breakthrough bleeding or spotting appears after some time during therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestagens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

Breast cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen, and possibly also oestrogen-only HRT that is dependent on the duration of taking HRT.

The Women's Health Initiative study (WHI) found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in the risk of having breast cancer diagnosed that is substantially lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

The excess risk becomes apparent after about 3 years of use but returns to baseline within a few (at most 5) years after stopping treatment.

HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5–10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies, including the WHI trial, suggest that the long-term use of combined HRT may confer a similar, or slightly smaller risk (see section 4.8).

Venous thromboembolism

HRT is associated with a 1.3 to 3-fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8).

Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m²) pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery, temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at a young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects), HRT is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT. Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic stroke

Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.

Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

Estrofem tablets contain lactose. Patients with rare hereditary galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (*Hypericum Perforatum*) may induce the metabolism of oestrogens.

Clinically, an increased metabolism of oestrogens may lead to decreased effect and changes in the uterine bleeding profile.

4.6 Fertility, pregnancy and lactation

Pregnancy

Estrofem is not indicated during pregnancy.

If pregnancy occurs during medication with Estrofem, treatment should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

Breast-feeding
Estrofem is not indicated during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical experience

In clinical trials less than 10% of the patients experienced adverse drug reactions. The most frequently reported adverse reactions are breast tenderness/breast pain, abdominal pain, oedema, and headache.

The adverse reactions listed below occurred in the clinical trials during Estrofem treatment.

System organ class	**Very common > 1/10**	**Common > 1/100; < 1/10**	**Uncommon > 1/1,000; < 1/100**	**Rare > 1/10,000; < 1/1,000**
Psychiatric disorders		Depression		
Nervous system disorders		Headache		
Eye disorders			Vision abnormal	
Vascular disorders			Venous embolism	
Gastrointestinal disorders		Abdominal pain or nausea	Dyspepsia, vomiting, flatulence or bloating	
Hepatobiliary disorders			Cholelithiasis	
Skin and subcutaneous tissue disorders			Rash or urticaria	
Musculoskeletal and connective tissue disorders		Leg cramps		
Reproductive system and breast disorders		Breast tenderness, breast enlargement or breast pain		
General disorders and administration site conditions		Oedema		
Investigations		Weight increased		

Post-marketing experience

In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported, and are by an overall judgment considered possibly related to Estrofem treatment. The reporting rate of these spontaneous adverse drug reactions is very rare (< 1/10,000, not known (cannot be estimated from the available data)). Post-marketing experience is subject to underreporting especially with regard to trivial and well-known adverse drug reactions. The presented frequencies should be interpreted in that light:

- Immune system disorder: Generalised hypersensitivity reactions (e.g. anaphylactic reaction/shock)
- Nervous system disorder: Deterioration of migraine, stroke, dizziness, depression
- Gastrointestinal disorder: Diarrhoea
- Skin and subcutaneous tissue disorders: Alopecia
- Reproductive system and breast disorders: Irregular vaginal bleeding*
- Investigations: Increased blood pressure.

The following adverse reactions have been reported in association with other oestrogen treatment:

- Myocardial infarction, congestive heart disease
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura, pruritus
- Vaginal candidiasis
- Oestrogen-dependent neoplasms benign and malignant. e.g. endometrial cancer (see section 4.4), endometrial hyperplasia or increase in size of uterine fibroids*
- Insomnia
- Epilepsy
- Libido disorder NOS (not otherwise specified)
- Deterioration of asthma
- Probable dementia (see section 4.4).

* In non-hysterectomised women

Breast cancer risk

Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.

The level of risk is dependent on the duration of use (see section 4.4).

Results of the largest randomised placebo-controlled trial (WHI study) and largest epidemiological study (MWS) are presented below.

Million Women Study – Estimated additional risk of breast cancer after 5 years' use

Age range (years)	**Cases per 1,000 never-users of HRT over a 5-year period***	**Risk ratio and 95% CI****	**Additional cases per 1,000 HRT users over 5 years' use (95% CI)**
Oestrogen-only HRT			
50-65	9-12	1.2	1-2 (0-3)
Combined oestrogen-progestagen			
50-65	9-12	1.7	6 (5-7)
* Taken from baseline incidence rates in developed countries. ** Overall risk ratio. The risk ratio is not constant but will increase with increasing			

duration on use. Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionally.

US WHI Studies – Additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 HRT users over 5 years (95% CI)
CEE oestrogen-only			
50-79	21	0.8 (0.7-1.0)	-4 (-6-0)*
CEE+MPA oestrogen-progestagen**			
50-79	17	1.2 (1.0-1.5)	4 (0-9)
* WHI study in women with no uterus which did not show an increase in risk of breast cancer. ** When the analysis was restricted to women who had not used HRT prior to the study, there was no increased risk apparent during the first 5 years of treatment. After 5 years the risk was higher than in non-users.			

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1,000 women with a uterus not using HRT.

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiological studies varied from between 5 and 55 extra cases diagnosed in every 1,000 women between the ages of 50 and 65.

Adding a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of 5 years of combined (sequential or continuous) HRT did not increase the risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer risk

Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study, 5 years of HRT resulted in 1 extra case per 2,500 users.

Risk of venous thromboembolism

HRT is associated with a 1.3 to 3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see section 4.4). Results of the WHI studies are presented below.

WHI Studies – Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 HRT users over 5 years (95% CI)
Oral oestrogen-only*			

50-59	7	1.2 (0.6-2.4)	1 (-3-10)
Oral combined oestrogen-progestagen			
50-59	4	2.3 (1.2-4.3)	5 (1-13)
* Study in women with no uterus			

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

The use of oestrogen-only and oestrogen-progestagen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

This relative risk is not dependent on age or on duration of use, but the baseline risk is strongly age-dependent. The overall risk of stroke in women who use HRT will increase with age (see section 4.4).

WHI Studies Combined – Additional risk of ischaemic stroke* over 5 years' use

Age range (years)	**Incidence per 1,000 women in placebo arm over 5 years**	**Risk ratio and 95% CI**	**Additional cases per 1,000 HRT users over 5 years (95% CI)**
50-59	8	1.3 (1.1-1.6)	3 (1-5)

* No differentiation was made between ischaemic and haemorrhagic stroke.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Overdosage may be manifested by nausea and vomiting. There is no specific antidote and treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural and semisynthetic estrogens, plain, ATC code: G03CA03.

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.

Relief of menopausal symptoms is achieved during the first few weeks of treatment.

5.2 Pharmacokinetic properties

Novo Nordisk's orally administered micronised 17β-estradiol as contained in Estrofem is rapidly and efficiently absorbed from the gastrointestinal tract, reaching a peak plasma concentration of

approximately 44 pg/ml (range 30-53 pg/ml) within 4-6 hours after intake of 2 mg. 17β-estradiol has a half life of approximately 14-16 hours. More than 90% of 17β-estradiol is bound to plasma proteins.

17β-estradiol is oxidised to estrone, which in turn is converted to estrone sulphate. Both transformations take place mainly in the liver. Oestrogens are excreted into the bile and then undergo reabsorption from the intestine. During this enterohepatic circulation, degradation occurs. 17β-estradiol and its metabolites are excreted in the urine (90-95%) as biologically inactive glucuronide and sulphate conjugates or in the faeces (5-10%) mostly unconjugated.

5.3 Preclinical safety data

Acute toxicity of oestrogens is low. Because of marked differences between animal species and between animals and humans preclinical results possess a limited predictive value for the application of oestrogens in humans.

In experimental animals estradiol or estradiol valerate displayed an embryolethal effect already at relatively low doses; malformations of the urogenital tract and feminisation of male fetuses were observed.

Preclinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential revealed no particular human risks beyond those discussed in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablet cores of both strengths contain:
Lactose monohydrate
Maize starch
Hydroxypropylcellulose
Talc
Magnesium stearate

Film-coating:
Estrofem 1 mg: Hypromellose, red iron oxide (E172), titanium dioxide (E171), propylene glycol and talc.
Estrofem 2 mg: Hypromellose, indigo carmine (E132), talc, titanium dioxide (E171) and macrogol 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not refrigerate.

6.5 Nature and contents of container

1 x 28 tablets or 3 x 28 tablets in calendar dial packs.

Calendar pack with 28 tablets consists of the following three 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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBERS

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: DD month YYYY
Date of latest renewal: DD month YYYY

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

MM/YYYY

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Estrofem 1 mg
film-coated tablets
estradiol

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains: estradiol 1 mg (as estradiol hemihydrate)

3. LIST OF EXCIPIENTS

Excipients include lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

1 x 28 film-coated tablets
3 x 28 film-coated tablets

5. METHOD AND ROUTE 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, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate

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

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Estrofem 1 mg
film-coated tablets
Estradiol 1 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

Excipients include lactose monohydrate. See leaflet for further information

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Estrofem 2 mg
film-coated tablets
estradiol

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Excipients include lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

1 x 28 film-coated tablets
3 x 28 film-coated tablets

5. METHOD AND ROUTE 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, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate

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

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

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15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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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

Excipients include lactose monohydrate. See leaflet for further information

PACKAGE LEAFLET

Package leaflet: Information for the user

Estrofem 1 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

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.

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.

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
- 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. Talk 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 suggests that taking combined oestrogen-progestagen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

For women who have had their womb removed and who are using oestrogen-only HRT for 5 years, little or no increase in breast cancer risk is shown.

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 oestrogen-progestagen HRT over 5 years, there will be 13 to 23 cases in 1,000 users (i.e. 4 to 6 extra 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.

Ovarian cancer
Ovarian cancer is rare. A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years.

Women aged 50 to 69 who are not taking HRT, on average, about 2 women in 1,000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for over 5 years, there will be between 2 and 3 cases per 1,000 users (i.e. up to 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. 5 extra 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. 3 extra 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. Talk 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*).

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 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 an intolerance to some sugars, contact your doctor before taking Estrofem.

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. Talk 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.

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
- Oedema (retention of fluid)
- Weight increase.

Uncommon side effects (may affect up to 1 in 100 people)
- 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)
- Irregular vaginal bleeding*
- Migraine, worse than before
- Stroke
- 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

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 the national reporting system. 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.

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 1 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), propylene glycol and red iron oxide (E172).

What Estrofem looks like and contents of the pack
The film-coated tablets are red, round with a diameter of 6 mm. The tablets are imprinted NOVO 282 on one side.

Pack sizes available:

- 1 x 28 film-coated tablets
- 3 x 28 film-coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
[To be completed nationally]

This medicinal product is authorised in Member States of the EEA under the following names:

Austria, Belgium, Croatia, Denmark, Finland, Iceland, Luxembourg, Portugal: Estrofem 1 mg

Germany: Estrifam 1 mg

This leaflet was last revised in MM/YYYY

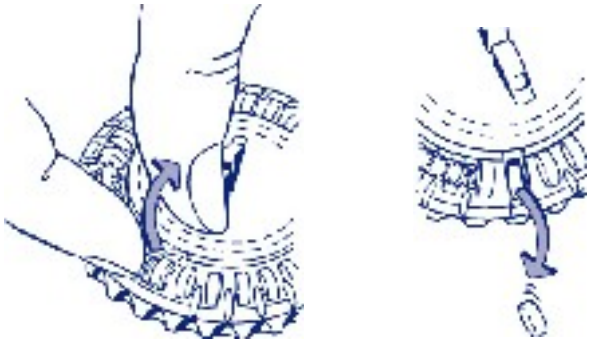
Other sources of information
Detailed information on this medicine is available on the web site of {MS/Agency}:

USER INSTRUCTIONS

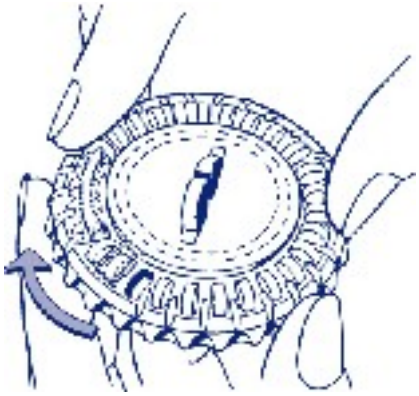
How to use the calendar pack

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 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.



Package leaflet: Information for the user

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

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.

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.

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
- 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. Talk 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 suggests that taking combined oestrogen-progestagen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

For women who have had their womb removed and who are using oestrogen-only HRT for 5 years, little or no increase in breast cancer risk is shown.

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 oestrogen-progestagen HRT over 5 years, there will be 13 to 23 cases in 1,000 users (i.e. 4 to 6 extra 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.

Ovarian cancer
Ovarian cancer is rare. A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years.

Women aged 50 to 69 who are not taking HRT, on average, about 2 women in 1,000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for over 5 years, there will be between 2 and 3 cases per 1,000 users (i.e. up to 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. 5 extra 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. 3 extra 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. Talk 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*).

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 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 an intolerance to some sugars, contact your doctor before taking Estrofem.

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. Talk 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.

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
- Oedema (retention of fluid)
- Weight increase.

Uncommon side effects (may affect up to 1 in 100 people)
- 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)
- Irregular vaginal bleeding*
- Migraine, worse than before
- Stroke
- 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

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 the national reporting system. 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.

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 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 sizes available:

- 1 x 28 film-coated tablets
- 3 x 28 film-coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
[To be completed nationally]

This medicinal product is authorised in Member States of the EEA under the following names:

Croatia, Denmark, Iceland, Portugal: Estrofem 2 mg

Germany: Estrifam 2 mg

This leaflet was last revised in MM/YYYY

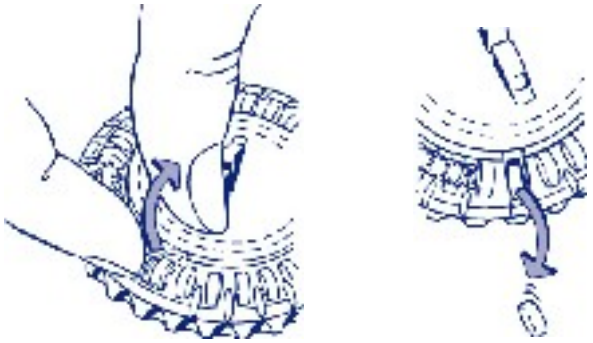
Other sources of information
Detailed information on this medicine is available on the web site of {MS/Agency}:

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 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.