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.
Prevention of osteoporosis in postmenopausal women at high risk of future fractures, who are tolerant of, or contraindicated for other medicinal products approved for the prevention of osteoporosis.
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.
Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.
Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with 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).

Smoking
This product should not be prescribed to a woman who is a smoker, espcially if she is older than 35, without careful medical evaluation

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		

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
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

Use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).
A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2,000 users. 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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

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

Store below 25 °C. 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. Registration number:

Estrofem® 1mg: 117-54-29845-00
Estrofem® 2mg: 060-75-27769-10

8. Manufacturer:
Novo Nordisk A/S
Novo Allé
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Denmark

9. Marketing Authorisation Holder:
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The content of this leaflet was checked and approved by the Ministry of Health in August 2016.