IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0218/050/002
Case No: 2067320

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Novo Nordisk A/S

Novo Alle, **DK-2880**, **Bagsvaerd**, **Denmark**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Estrofem 1mg film-coated tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **20/07/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Estrofem 1mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains estradiol 1 mg as estradiol hemihydrate.

Excipients: lactose monohydrate 37.3mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Red, film-coated, biconvex tablets, engraved with NOVO 282, diameter 6 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms.

In women with intact uterus, progestogen therapy should be added.

The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Estrofem is an oestrogen-only product for hormonal replacement. 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 of Estrofem could be indicated if the response after three months is insufficient for satisfactory relief of symptoms.

Estrofem is administered orally, one tablet daily without interruption. Treatment of hysterectomised women and postmenopausal women may be started on any convenient day. If the woman is menstruating, treatment is started on day 5 of bleeding. In women with an intact uterus a progestogen must be added for 12-14 days every month/28-day cycle. The progestogen type, dose, as well as the duration of progestogen administration should provide a sufficient inhibition of the oestrogen-induced endometrial proliferation *(see section 4.4)*

If the patient has forgotten to take one tablet, the forgotten tablet is to be discarded. Forgetting a dose for non-hysterectomised women may increase the likelihood of breakthrough bleeding and spotting.

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

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected oestrogen-dependant malignant tumours (e.g endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Active or recent arterial thromboembolic disease (angina, myocardial infarction);
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;
- Known hypersensitivity to the active substance or to any of the excipients;
- Porphyria

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely effect the 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.

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 shoul be guided by this and by the contra-indications 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 that changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, 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 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
- A history of, or risk factors for, thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g 1st degree heredity for breast cancer;
- Liver disorders (e.g. liver adenoma);
- Hypertension
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systematic 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

Women with an intact uterus with abnormal bleeding of unknown aetiology or women with an intact uterus who have previously been treated with unopposed oestrogens should be examinded with special care in order to disclose a possible hyperstimulation/malignancy of the endometium before initiation of treatment with Estrofem.

The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods *(see section 4.8).* The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.

For oral doses of estradiol >2mg the endometrial safety of added progestogens has not been studied.

Breakthrough bleeding and spotting may occur during the first months of treatment in women with an intact uterus. If breakthrough bleeding or spotting occurs after some time on 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 progestogens to oestrogen replacement therapy is recommended in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

Breast cancer

A randomized placebo-controlled trial the Women's Health Initiative (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years *(see section 4.8).* For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in the risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.
HRT, especially oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e deep vein thrombosis or pulmonary embolism. One randomized controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users, it is estimated that the number of cases of VTE that will occur over a five year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (Body Mass Index > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all post-operative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible. Treatment should not be started until the woman is completely mobilized.

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

Coronary arerty disease (CAD)

There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomized controlled trials examining effects in cardiovascular morbidity or mortality. Therefore it is uncertain whether these findings extend to other HRT products.

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5-year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 aged 60-69 years. It is estimated for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer

Long term (at least 5-10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of overian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than oestrogen-only products.

Other conditions

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed since it is expected that the level of circulating active ingredient in Estrofem will be increased.

- Women with pre-existing hypertriglyceridemia should be followed closely during 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 (TGB), 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 TGB. 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 increase circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/rennin substrate, alpha-1-antitrypsin, ceruloplasmin).

- Estrofem has no contraceptive effect. Hormonal contraception should be stopped when the use of Estrofem is started and the patent should be advised to take non-hormonal contraceptive precautions if required.

- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

- Estrofem tablets contain lactose. Patients with rare hereditary problems of 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 (and progestogens) 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, carbamezapin) 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 including St. John's Wort (*Hypericum perforatum*) may induce the metabolism of oestrogens (and progestogens).

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

4.6 Pregnancy and lactation

Estrofem is not indicated during pregnancy. If pregnancy occurs during medication with Estrofem treatment should be withdrawn immediately. The results of epidemiological studies to-date relevant to inadvertent foetal exposure to combinations of oestrogens and progestogens indicate no teratogenic or foetotoxic effect.

Estrofem is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No effects known.

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 may occur during Estrofem treatment:

System Organ Class	Very common >1/10	Common >1/100, <1/10	Uncommon >1/1000, <1/100	Rare (>1/10,000, <1/1000)
Psychiatric disorders		Depression		
Nervous system disorder		Headache		
Eye disorder			Vision abnormal NOS	
Vascular disorders			Venous embolism NOS	
Gastrointestinal disorders		Abdominal pain or nausea	Dyspepsia, vomiting, flatulence or bloating	
Hepatobiliary disorders			Cholelithiasis	
Skin and subcutaneous tissue disorders			Rash or urticaria	
Musculosketal 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		

Breast cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk or breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For *oestrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women study (MWS) are similar at 1.35 (95% CI: 1.21-1.49) and 1.30 (95% CI: 1.21-1.40), respectively.

For *oestrogen plus progestogen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.
The MWS reported that, compared to never users, the use of various types of oestrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95% CI: 1.88-2.12) than use of oestrogens alone (RR = 1.30, 95% CI: 1.21-1.40) or use of tibolone (RR = 1.45, 95% CI: 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95% CI: 1.01-1.54) after 5.6 years of use of oestrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:
- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 current or recent users of HRT, the number of *additional* cases during the corresponding period will be
- For users of *oestrogen-only* replacement therapy,
  - between 0 and 3 (best estimate = 1.5) for 5 years' use
  - between 3 and 7 (best estimate = 5) for 10 years' use
- For users of *oestrogen plus progestogen* combined HRT
  - between 5 and 7 (best estimate = 6) for 5 years' use
  - between 18 and 20 (best estimate = 19) for 10 years' use

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *oestrogen-progestogen combined* HRT (CEE + MPA) per 10,000 women years. According to calculations from the trial data, it is estimated that:
- For 1000 women in the placebo group,
  - About 16 cases of invasive breast cancer would be diagnosed in 5 years
- For 1000 women who used oestrogen + progestogen combined HRT (CEE + MPA), the number of additional cases would be:
  - Between 0 and 9 (best estimate =4) for 5 years' use

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) *(see section 4.4)*

<u>Endometrial cancer</u>

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies. The best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expeted to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2- to 12-fold greater compared with non-users. Adding a progestogen to oestrogen-only therapy greatly reduces this increased risk.

Post-marketing experience:

In addition to the above-mentioned adverse drug reactions, those presented below have been spontaneously reported, and are by an overall judgement considered possibly related to Estrofem treatment. The reporting rate of these spontaneous adverse drug reactions is very rare (<1/10,000 patient years). Post-marketing experience is subject to under-reporting especially with regard to trivial and reactions well-known adverse drug. The presented frequencies should be interpreted in that light:
- Reproductive system and breast disorders: Irregular vaginal bleeding*
- Nervous system disorders: Deterioration of migraine, stroke, dizziness, depression
- Gastrointestinal disorder: Diarrhoea
- Skin and subcutaneous tissue disorders: Alopecia
- Investigations: Increased blood pressure

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

- Myocardial infarction, congestive heart disease
- Gallbladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura, pruritis
- Vaginal candidiasis
- Risk of developing 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

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

ATC code: G03C A03
Oestrogen – only product for continuous hormone replacement therapy (HRT).

The active ingredient, synthetic 17ß-estradiol, is chemically and biologically identical to endogenous human oestradiol. 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.

Endogenous 17ß-estradiol induces and maintains the primary and secondary sexual characteristics. The biological effect of 17ß-estradiol is carried out through a number of specific estrogen receptors. The steroid receptor complex is bound to the cell's DNA and induces synthesis of specific proteins

17β-oestradiol increases SHBG-BC (sex-hormone-binding-globulin binding capacity) and CBG-BC (corticosteroid-binding-globulin binding capacity). The gonadotrophins FSH (follicle stimulating hormone) and LH (luteinizing hormone) are suppressed.`

5.2 Pharmacokinetic properties

Novo Nordisk's orally administered micronised 17β-oestradiol as contained in Estrofem is rapidly and efficiently absorbed from the gastrointestinal tract, reaching a peak plasma concentration of approximately 44pg/ml (range 30-53 pg/ml) within 6 hours after intake of 2mg. 17β-oestradiol has a half life of approximately 18 hours. More than 90% of 17β-oestradiol is bound to plasma proteins.

17β-oestradiol is oxidised to oestrone, which in turn is converted to oestrone 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-oestradiol 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 humans preclinical results possess a limited predictive value for the application of oestrogens to humans.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Hydroxypropylcellulose
Talc
Magnesium stearate
Hypromellose
Red iron oxide (E172)
Titanium dioxide (E171)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light. Do not refrigerate or freeze.

6.5 Nature and contents of container

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 white non-transparent polystyrene.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Alle
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8 MARKETING AUTHORISATION NUMBER

PA 0218/050/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 February 1998

Date of last renewal: 06 February 2008

10 DATE OF REVISION OF THE TEXT

July 2010