

# New Zealand Datasheet

## Name of Medicine

ESTROFEM®

17 $\beta$ -oestradiol

## Presentation

**Estrofem 1 mg** calendar dial pack contains 28 tablets as described below:

28 red, round, film coated tablets with diameter 6mm and stamped "Novo 282" on one side. The other side is plain. Each tablet contains 1mg of 17 $\beta$ -oestradiol and weighs about 80mg.

**Estrofem 2 mg** calendar dial pack contains 28 tablets as described below:

28 blue, round, film coated tablets with diameter 6mm and stamped "Novo 280" on one side. The other side is plain. Each tablet contains 2mg of 17 $\beta$ -oestradiol and weighs about 80mg.

## Uses

### Actions

Pharmacotherapeutic group: Natural and semisynthetic oestrogens, plain, ATC code G03C A03

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

Oestrogens prevent bone loss following menopause or ovariectomy.

Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestagen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

The effects of Estrofem on bone mineral density were examined in a 2-year randomized, double-blind, placebo-controlled trial in early postmenopausal women (n=166, including 41 on Estrofem 1mg and 42 on Estrofem 2 mg). Estrofem 1 mg and 2 mg significantly prevented bone loss at the lumbar spine and total hip in comparison with the placebo-treated women. The overall difference in mean percentage change in bone mineral density versus placebo was for 1 mg and 2 mg respectively 4.3% and 5.3% at the lumbar spine, 4.0% and 3.9% at the femoral neck. The corresponding numbers for the trochanter were 3.3% and 3.2% after 2 years of treatment.

The percentage of women who maintained or gained BMD in lumbar zone during treatment was 61% and 68% in women treated with 1 mg and 2 mg Estrofem respectively.

### Pharmacokinetics

Following oral administration of 17 $\beta$ -oestradiol in micronised form, rapid absorption from the

gastrointestinal tract occurs. It undergoes extensive first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 44 pg/ml (range 30-53 pg/ml) within 6 hours after intake of 2 mg. The half-life of 17 $\beta$ -oestradiol is about 18 hours. It circulates bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound. Metabolism of 17 $\beta$ -oestradiol occurs mainly in the liver and the gut but also in target organs, and involves the formation of less active or inactive metabolites, including estrone, catecholestrogens and several oestrogen sulphates and glucuronides. Oestrogens are excreted with the bile, where they are hydrolysed and reabsorbed (enterohepatic circulation), and mainly in urine in biologically inactive form.

### **Indications**

Estrofem is indicated for treatment of oestrogen deficiency syndrome, including prevention of bone mineral content loss in postmenopausal women at increased risk of developing fractures.

Estrofem is particularly for women who have been hysterectomised and therefore do not require combined oestrogen/progestagen therapy. In women with an intact uterus, use of opposed therapy must be considered.

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

### **Dosage and Administration**

Estrofem is an oestrogen-only product for hormonal replacement. Estrofem should not be administered to women with an intact uterus unless combined with a suitable progestagen regimen during at least the last 10-12 days of each cycle. For initiation and continuation of treatment of menopausal symptoms, the lowest effective dose for the shortest duration (see also Warnings and Precautions) 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. Prevention of bone mineral content loss is normally achieved with 1-2 mg estradiol daily, therefore higher doses are not usually used for long term prophylaxis of osteoporosis.

Estrofem is administered orally, one tablet daily without interruption. In women with amenorrhoea and not taking HRT, women transferring from another oestrogen only HRT product, treatment with Estrofem may be started on any convenient day.

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next twelve hours. Otherwise the missed tablet should be discarded and the patient advised to continue with the next day's tablet.

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

### **Contraindications**

- Known hypersensitivity to the active substance or the excipients
- Known, past or suspected breast cancer
- Known, past or suspected oestrogen dependent neoplasia eg. endometrial cancer
- Porphyria
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Active or recent arterial thromboembolic diseases (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

## **Warnings and Precautions**

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. All prospective and current users should be informed of these risks and benefits. The need for treatment with HRT should be reviewed on a yearly basis and include a physical and gynaecological examination. HRT should be used only in women with menopausal symptoms and ordinarily not for the long term maintenance of general health as the risks of long term treatment with HRT in most circumstances outweigh the benefits. HRT should be prescribed at the lowest effective doses and for the shortest duration (generally not longer than 3-4 years), consistent with the treatment goals and risks for the individual women.

As a general rule, HRT should not be prescribed for longer than one year without another physical examination including gynaecological examination being performed. Also the lowest dose which alleviates the symptoms should be prescribed for the shortest possible time. In most circumstances, the risks of long-term HRT treatment outweigh the benefits and combined HRT should not be used for longer than 3-4 years.

### Medical examination/follow-up

Before initiating or reinstating 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 section 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 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
- 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
- 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

Women with intact uterus who have previously been treated with unopposed oestrogens should be examined with special care in order to disclose a possible hyperstimulation/malignancy of the endometrium 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 Adverse Effects). The addition of a progestagen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk. Close clinical surveillance of all women taking oestrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" oestrogens results in a different endometrial risk profile than synthetic oestrogens of equivalent oestrogen dose.

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

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears 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 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

A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Woman Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestagen combinations or tibolone for HRT for several years (see Adverse Effects). 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 progestagen was added, either sequentially or continuously, and regardless of type of progestagen. There was no evidence of a difference in 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-progestagen 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 randomised controlled trial and epidemiological studies found a two- to three-fold 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 5 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<sup>2</sup>) 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 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 postoperative 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 restarted until the woman is completely mobilised.

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, dyspnea).

### Coronary artery disease (CAD)

There is no evidence from randomised 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 oestrogen/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 randomised controlled trials examining effects in cardiovascular morbidity or mortality. In the absence of comparable data, these risks should be assumed to be similar.

For the WHI study, a global index summarising the balance of risks and benefits included an analysis of the 2 primary outcomes, invasive breast cancer and CHD, and the following secondary outcomes: stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. The women enrolled in the study had a mean age at entry of 63.3 years. On average they were overweight (mean body mass index [BMI] = 28.5) and one-third were obese (BMI ≥ 30), 50% were previous or current smokers, one-third had received treatment for high blood pressure and over 10% had raised cholesterol levels requiring medication.

The oestrogen plus progestagen arm of the WHI study was prematurely stopped after an average follow-up of 5.2 years, based on the finding of increased breast cancer risk. The

study also found increases in coronary heart disease, stroke, and pulmonary embolism in study participants on oestrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of oestrogen plus progestagen, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefit (NHLBI press release July 9 2002).

**Table 1: Increased Risks**

	Relative Risk (RR)	Placebo arm: Cases/10000	CEE + MPA arm: Cases/10000	Increased Absolute Risk per 10000 women / year
Breast Cancer	1.26	30	38	8
Stroke	1.41	21	29	8
CHD	1.29	30	37	7
Thromboembolic Events (blood clots in legs and lungs)	2.11	16	34	18

**Table 2: Decreased Risks**

	Relative Risk (RR)	Placebo arm: Cases/10000	CEE + MPA arm: Cases/10000	Decreased Absolute Risk per 10000 women / year
Colorectal Cancer	0.63	16	10	6
Hip Fractures	0.66	15	10	5
Total Fractures	0.76	191	147	44

### 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 women aged 60-69 years. It is estimated that 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 and oestrogen plus progestagen HRT products in women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRTs confers to 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 ingredients in Estrofem will increase.

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-1-antitrypsin, ceruloplasmin).

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 monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine

### Use in 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.

### Use in Lactation

Estrofem is not indicated during lactation.

### Effects on Ability to Drive and Use Machines

No effects known.

### Adverse 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 ≥1/1,000; <1/100	Rare ≥1/10,000; <1/1,000
Psychiatric disorders		Depression		
Nervous system disorders		Headache		
Eye disorders			Vision abnormal NOS.	
Vascular disorders			Venous embolism NOS	

<b>System organ class</b>	<b>Very common ≥1/10</b>	<b>Common ≥1/100; &lt;1/10</b>	<b>Uncommon ≥1/1,000; &lt;1/100</b>	<b>Rare ≥1/10,000; &lt;1/1,000</b>
<b>Gastrointestinal disorders</b>		Abdominal pain or nausea	Dyspepsia, vomiting, flatulence or bloating	
<b>Hepatobiliary disorders</b>			Cholelithiasis	
<b>Skin and subcutaneous tissue disorders</b>			Rash or urticaria	
<b>Musculoskeletal and connective tissue disorders</b>		Leg cramps		
<b>Reproductive system and breast disorders</b>		Breast tenderness, breast enlargement or breast pain		
<b>General disorders and administration site conditions</b>		Oedema		
<b>Investigations</b>		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 of 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 progestagen 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-progestagen 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-progestagen 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 progestagen 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-progestagen 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 + progestagen 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 Warnings and Precautions).

#### Endometrial cancer

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 expected 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 progestagen 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 judgment considered possibly related to Estrofem treatment. The reporting rate of these spontaneous adverse drug reactions is very rare (<1/10,000). 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: Generalized hypersensitivity reactions (e.g. anaphylactic reaction/shock)
- Reproductive system and breast disorders: Irregular vaginal bleeding\*
- 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 Warnings and Precautions), endometrial hyperplasia or increase in size of uterine fibroids\*
- Insomnia
- Epilepsy
- Libido disorder NOS (not otherwise specified)
- Deterioration of asthma
- Probable dementia (see Warnings and Precautions)

\* In non-hysterectomised woman

## Interactions

The metabolism of oestrogens and progestagens 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, carbamazepin) 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.

## Overdosage

### Symptoms

Nausea and vomiting.

### Treatment

There is no specific antidote and treatment should be symptomatic.

## Pharmaceutical Precautions

Store below 25°C

Do not refrigerate

Store in a dry place

Protect from light

Keep out of reach of children.

## Medicine Classification

Prescription Medicine.

## Package Quantities

Estrofem 1mg and 2mg tablets are supplied in a calendar dial pack containing 28 tablets.

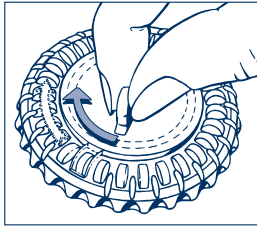
## Further Information

### Nature of the container

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

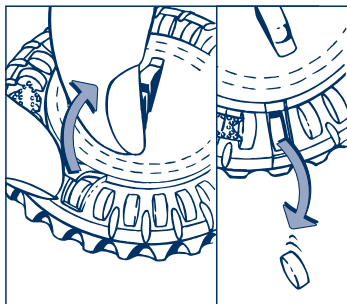
- The base made of coloured non-transparent polypropylene
- The ring-shaped lid made of transparent polystyrene
- The centre-dial made of coloured non-transparent polystyrene.

### Instructions for use

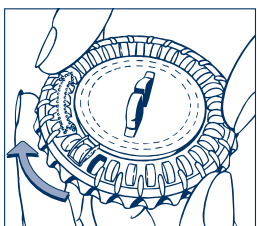


The first tablet to be taken is under the sealed opening in the see-through outer rim of the pack.

Turn the inner white disc of the pack until the day of the week on which the first tablet is to be taken is next to the little plastic tab.



Break off the plastic tab using a finger nail and remove the first tablet from the pack. The see-through dial can only be turned after the tablet in the opening has been removed.



Each day turn the see-through dial clockwise one place to obtain the next tablet. Continue until all tablets have been taken.

### List of excipients

Lactose monohydrate

Maize starch

Gelatin

Talc

Magnesium Stearate

Titanium Dioxide E171

Hypromellose

Propylene glycol (Estrofem 1 mg only)  
Macrogol 400 (Estrofem 2 mg only)  
Indigo carmine E132 (Estrofem 2 mg only)  
Red iron oxide E172 (Estrofem 1 mg only)

### **Preclinical safety data**

The toxicity profile of estradiol is well known. There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the datasheet.

### **Name and Address**

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Auckland

Tel: (09) 916 5590

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### **Date of Preparation**

1 October 2009

Estrofem is a trade name owned by Novo Nordisk FemCare AG