New Zealand Datasheet

1 PRODUCT NAME
ESTROFEM®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
17ß-oestradiol 1 mg and 2 mg tablets.

3 PHARMACEUTICAL FORM
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 17ß-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 17ß-oestradiol and weighs about 80mg.

4 CLINICAL PARTICULARS
4.1 Therapeutic 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 treating women older than 65 years is limited.

4.2 Dose 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 3 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.

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 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 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
- Known thrombophilic disease disorders (e.g. protein C, protein S, or antithrombin deficiency (see section 4.4)

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. 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 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.

<u>Medical examination/follow-up</u>

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.

<u>Conditions which need supervision</u>

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
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.

In women with an 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. 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.

Breakthrough bleeding and spotting may occur during the first months of treatment. 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 shows an increased risk of breast cancer in women taking combined oestrogen-progestagen or 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 womenusing oestrogen-only HRT. Observational studies have mostly reported a small increase in the risk of having breast cancer diagnosed that is lower than that found in users of oestrogen-progestagen combinations (see section 4.8). Results from a large meta-analysis showed that after stopping treatment the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

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.

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/m^2), 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, dyspnea).

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.

Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

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

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).

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

4.5 Interaction with other medicines and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Effects on Fertility
Not applicable

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 breast-feeding.

4.7 Effects on ability to drive and use machines
Estrofem has no known effects 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 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	
Vascular disorders			Venous embolism	
Gastrointestinal disorders		Abdominal pain or nausea	Dyspepsia, vomiting, flatulence or bloating	
Hepatobiliary disorders			Cholelithiasis	
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		

Breast cancer
The increased risk in users of oestrogen-only therapy is 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)
.

Absolute risk estimates based on results of the largest randomised placebo-controlled trial (WHI study) and the largest meta-analysis of prospective epidemiological studies are presented below.

Largest meta-analysis of prospective epidemiological studies

Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1,000 never-users of HRT over a 5-year period (50-54 years) *	Risk ratio	Additional cases per 1,000 HRT users after 5 years
Oestrogen-only HRT			
50	13.3	1.2	2.7
Combined oestrogen-progestagen			
50	13.3	1.6	8.0
* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2). Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionally.			

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1,000 never-users of HRT over a 10-year period (50-54 years) *	Risk ratio	Additional cases per 1,000 HRT users after 10 years
Oestrogen-only HRT			
50	26.6	1.3	7.1
Combined oestrogen-progestagen			
50	26.6	1.8	20.8
* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2). 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.			

<u>Endometrial cancer</u>
<u>Postmenopausal women with a uterus</u>

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.

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 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 woman

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 https://nzphvc.otago.ac.nz/reporting.

4.9 Overdose

Symptoms
Nausea and vomiting.

Treatment
There is no specific antidote and treatment should be symptomatic. For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The active ingredient, synthetic 17β-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.

5.2 Pharmacokinetic properties

Following oral administration of 17β-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 17β-oestradiol is about 18 hours. It circulates bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound. Metabolism of 17β-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, catecholoestrogens and several oestrogen sulfates and glucuronides. Oestrogens are excreted by the bile, where they are hydrolysed and reabsorbed (enterohepatic circulation), and mainly in urine in biologically inactive form.

5.3 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.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate
Maize starch
Hydroxypropylcellulose
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)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
The shelf-life for Estrofem tablets is 48 months.

6.4 Special precautions for storage
Store below 25ºC
Do not refrigerate
Store in a dry place
Protect from light
Keep out of reach of children.

6.5 Nature and contents of container
Estrofem 1mg and 2mg tablets are supplied in a calendar dial pack containing 28 tablets.

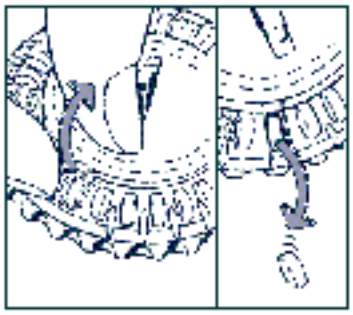
Nature of the container
The calendar dial pack with 28 tablets consists of the following three parts:

- 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.

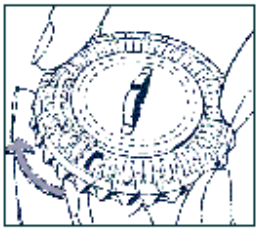
Instructions for use

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.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Novo Nordisk Pharmaceuticals Ltd
PO Box 51-268
Pakuranga
Auckland

Tel: (09) 916 5590
Fax: (09) 916 5595

9 DATE OF FIRST APPROVAL

Estrofem 1 mg: 23 October 1996
Estrofem 2 mg: 13 November 1992

10 DATE OF REVISION OF THE TEXT

8 September 2020
CCDS V 16.0

Estrofem is a trade name owned by Novo Nordisk Health Care AG

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Updated information on breast cancer risk
4.8	Updated information on breast cancer risk