AUSTRALIAN PRODUCT INFORMATION

ESTROFEM® estradiol (as hemihydrate) 1 mg tablet dial dispenser pack
ESTROFEM® estradiol (as hemihydrate) 2 mg tablet dial dispenser pack

1. NAME OF THE MEDICINE

Estradiol hemihydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Estrofem is an estrogen preparation comprising 28 tablets. Each tablet contains 1 mg or 2 mg estradiol (as hemihydrate). The estrogen component of Estrofem substitutes for the loss of endogenous estrogen production due to natural or surgical menopause in hysterectomised women.

Excipient with known effect: lactose monohydrate. For the full list of excipients, see 'Section 6.1 List of Excipients.'

3. PHARMACEUTICAL FORM

Film coated tablet.

Estrofem 1 mg are red tablets marked NOVO 282 on one side, blank on the other side, with a diameter of 6 mm.

Estrofem 2 mg are blue tablets marked NOVO 280 on one side, blank on the other side, with a diameter of 6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short term symptomatic treatment of estrogen deficiency due to natural or surgical menopause in hysterectomised postmenopausal women (see 'Section 4.2 Dose and Method of Administration' and 'Section 5.1 Pharmacodynamic Properties' - 'Clinical trials').

In women with intact uteri, use of opposed therapy must be considered.

4.2 Dose and Method of Administration

Dosage

The initial dose for relief of symptoms of estrogen deficiency is 1 mg or 2 mg daily.

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

In postmenopausal women with normal uteri Estrofem should be given with a progestagen for at least 10 consecutive days of the 28 day cycle. This will usually induce a withdrawal bleed.

In hysterectomised post-menopausal women Estrofem may be started on any convenient day. In oligomenorrhoea, treatment should be started on day 5 of bleeding.

If symptoms such as hot flushes have ceased, consideration of transferring to local vaginal treatment should be given if troublesome local symptoms remain.

Duration of therapy
HRT should be prescribed at the lowest effective dose and for shortest duration (see 'Section 4.4 Special Warnings and Precautions for Use'). The continuation of the treatment should be re-evaluated annually. Women who have undergone a premature menopause may require longer term treatment.

Method of Administration
Estrofem is administered orally, without chewing, one tablet daily without interruption preferably at the same time each day.

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next 12 hours. Otherwise the missed tablet should be discarded and the patient advised to continue with the next day's tablet. Forgetting a dose for women with a uterus may increase the likelihood of breakthrough bleeding and spotting.

Use of the calendar dial pack
The first tablet to be taken is under the sealed opening in the transparent outer rim of the pack. Turn the inner disc of the pack until the day of the week on which the first tablet is to be taken is opposite the sealed opening. Lift off the plastic seal with a finger-nail and remove the first tablet from the pack. Each day, turn the transparent outer rim of the pack in the direction of the arrow to obtain the next tablet. Continue until all tablets have been taken.

4.3 Contraindications

- Known, suspected, or past history of breast cancer
- Known, suspected, or past history of estrogen-dependent neoplasia e.g. endometrial cancer
- Vaginal bleeding of unknown aetiology
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see 'Section 4.4 Special Warnings and Precautions for Use')
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease where liver function tests have failed to return to normal
- Known hypersensitivity to any of the components
- Porphyria
- Known or suspected pregnancy.

4.4 Special Warnings and Precautions for Use

HRT should not be initiated or continued to prevent or treat cardiovascular disease.

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. A careful appraisal of the risks and benefits should be undertaken at least annually.

HRT should be used only in women with menopausal symptoms and ordinarily not for long term use. HRT should be prescribed at the lowest effective doses and for the shortest duration 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.

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.

Medical examination/follow-up

Before initiating therapy, it is recommended that the woman is fully informed of all likely benefits and potential risks. Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examinations should be guided by this and by the contraindications and warnings for use. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination, including gynaecological and breast mammography examinations.

Women should be advised what changes in their breasts should be reported to their doctor or nurse (see the "Breast cancer" section below). Investigations including appropriate imaging tools e.g. 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
- Risk factors for, thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumours e.g. 1st degree heredity for breast cancer
- Hypertension
- Cardiac failure
- 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 contraindication is discovered or in the following situations:

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

Endometrial hyperplasia and carcinoma
For oral doses of estradiol >2 mg the endometrial safety of added progestagens has not been studied.

In women with an intact uterus endometrial assessment should be carried out if indicated; this may be particularly relevant in women who are, or who have been previously treated with estrogens unopposed by a progestagen.

Breakthrough bleeding and spotting may occur during the first months of treatment in women with intact uteri. 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 estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestagens to estrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis if they are known to have residual endometriosis.

Liver disease
Women with acute or chronic liver disease, or who have a history of liver disease where the liver function tests have failed to return to normal, should be monitored regularly with liver function tests before and during treatment with Estrofem.

Venous thromboembolism
HRT is associated with a 1.3- to 3-fold risk of developing venous thromboembolism (VTE), i.e. deep venous thrombosis or pulmonary embolism. The risk versus the benefits should therefore be carefully weighed in consultation with the individual woman when prescribing HRT to women with a risk factor for VTE. 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 Contraindications'). Generally recognised risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobilisation, pregnancy/postpartum period, cancer, a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), systemic lupus erythematosus (SLE) and obesity (BMI > 30 kg/m^2). The risk of VTE also increases with age. There is no consensus about the possible role of varicose veins in VTE.

The risk of VTE may be temporarily increased with prolonged immobilisation, major elective or post-traumatic surgery or major trauma. Depending on the nature of the event and the duration of the immobilisation, consideration should be given to a temporary discontinuation of HRT. 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).

Scarabin and others[5] reported the results of a case control study conducted during 1999-2002 in France. The investigators recruited 155 consecutive cases with a first documented episode of VTE of unknown cause (92 with pulmonary embolisms and 63 with deep venous thrombosis), and 381 controls (women admitted to hospital for other reasons) matched for centre, age, and time of recruitment. Overall, 32 (21%) cases and 27 (7%) controls were current users of oral estrogen replacement therapy (this was defined in this study as estrogen only therapy or combined HRT), whereas 30 (19%) cases and 93 (24%) controls were current users of transdermal estrogen replacement therapy. After adjustment for potential confounding variables, the odds ratio for VTE in current users of oral and transdermal estrogen replacement therapy compared with non-users was 3.5 (95% CI 1.8-6.8) and 0.9 (0.5-1.6), respectively. Estimated risk for VTE in current users of oral estrogen replacement therapy compared with transdermal estrogen replacement therapy users was 4.0 (1.9-8.3). These results may be interpreted as meaning that (i) the higher risk of VTE as shown in the WHI study has been further supported; and (ii) current use but not past use was a risk factor for VTE. Use in the first year was also more risky than later use, a finding that is also consistent with the WHI study.

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated estrogens 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 randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke

Combined estrogen-progestagen and estrogen-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 Adverse Effects (Undesirable Effects)').

In the WHI estrogen alone sub-study, a statistically significant increased risk of stroke was reported in women receiving daily conjugated estrogens (CE 0.625 mg) compared to placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated after the first year of treatment and persisted.

In the estrogen plus progestin sub-study of WHI, a statistically significant increased risk of stroke was reported in women receiving daily CE 0.625 mg plus medroxyprogesterone acetate (MPA 2.5 mg) compared to placebo (31 versus 24 per 10,000 women-years). The increase in risk was demonstrated after the first year of treatment and persisted. However, the secondary analysis of the WHI data showed that there was no risk of stroke in women aged 50-59 years.

The Nurses' Health Study however, showed that the reduction of the hormone dose leads to a reduction of stroke risk[6].

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 estrogen-only or combined estrogen-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 Adverse Effects (Undesirable Effects)').

An increased risk of ovarian cancer in menopausal women taking estrogen only replacement therapy (ERT) was observed in a large US prospective cohort observational study, which included over 44,000 women using ERT.

Women were either menopausal before the start of follow up or became menopausal during follow up, either naturally or as a result of hysterectomy (defined as simple hysterectomy or hysterectomy with unilateral oophorectomy). Mean age at the start of follow up was 56.6 years (range 36-89 years). These women were followed up for a mean duration of 13.4 years (range 1 month to 19.8 years).

Increasing duration of ERT use was significantly associated with ovarian cancer, with a 7% increase in rate ratio (RR) per year of use. The RR was 1.8 (95% CI, 1.1-3.0) for those who used ERT for 10 to 19 years and 3.2 (95% CI, 1.7-5.7) for those who used ERT for 20 or more years. This equates to approximately 3 and 9 additional cases per 10,000 women-years at these time points compared to an incidence of ovarian cancer in non-users of ERT in the study of 4.4 per 10,000 women-years. The increase in risk was greater in the subpopulation of women who were menopausal as a result of hysterectomy. In this subgroup the RR was 2.0 (95% CI, 0.96-4.3) for between 10 and 19 years of use and 3.4 (95% CI, 1.6-7.5) for 20 years of use or more.

Missing data for approximately two-thirds of ERT users precluded analysis of specific preparations or doses. The study authors noted that much of the long term use of ERT likely included higher average daily doses of estrogen than are currently recommended. The analysis could not determine whether duration, dose or duration and dose of ERT explained the elevated risks among long term users.

Endometrial cancer
Endometrial hyperplasia (atypical or adenomatous) often precedes endometrial cancer. In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens. 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 estrogen dose, the reported increase in endometrial cancer risk among unopposed estrogen users varies from 2-to 12-fold greater compared with non-users. After stopping treatment, risk may remain elevated for at least 10 years. The appropriate addition of a progestagen to an estrogen regimen lowers this additional risk.

Breast cancer
The overall evidence shows an increased risk of breast cancer in women taking estrogen-only HRT or estrogen-progestagen combinationsthat is dependent on the duration of taking HRT.

Combined estrogen-progestagen therapy:
The randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see 'Section 4.8 Adverse Effects (Undesirable Effects)').

Estrogen only therapy:
The WHI trial found no increase in the risk of breast cancer in hysterectomised women using estrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is lower than that found in users of estrogen-progestagen combinations (see 'Section 4.8 Adverse Effects (Undesirable Effects)').

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.

Mammographic density may be increased after the use of combined HRT. This may have implications for the sensitivity and specificity of breast cancer screening.

Regular breast examination and, where appropriate, mammography should be carried out in women on HRT. Breast status should also be closely monitored in women with a history of or known breast nodules, fibrocystic disease, or with a family history of breast cancer.

Dementia
See 'Section 5.1 Pharmacodynamic Properties' – 'Clinical trials' (WHIMS sub-study).

Other conditions
Estrofem has no contraceptive effect and will not restore fertility.

The risks and benefits in younger women receiving treatment for the short-term management of menopausal symptoms of estrogen deficiency or for the management of premature menopause were not examined in the WHI study. As well, the study did not include other formulations or dosage regimens, such as Novo Nordisk's products containing 17-beta-estradiol and norethisterone acetate, or other routes of administration of HRT.

In the absence of data specific to this product, if prescribing any form of hormone replacement therapy as primary prevention of osteoporosis, the potential for increased cardiovascular, thrombotic and neoplastic adverse events must be considered. Combined hormone replacement therapy should not be used for the long-term maintenance of general

health, including the primary prevention of cardiovascular disease. Estrogen or estrogenic compounds must not be used alone as estrogen replacement therapy in women who have not had a hysterectomy.

Estrogens 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 is increased.

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

Estrogens increases 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).

Use in elderly
Of the total number of subjects in the conjugated equine estrogens in combination with medroxyprogesterone acetate sub-study of the Women's Health Initiative study[(1)], 44% (n = 7,320) were 65 years and over, while 6.6% (n = 1,095) were 75 and over. No significant differences in overall safety were observed between subjects 65 years and over compared to younger subjects. There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to younger subjects.

HRT use does not improve cognitive function. In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed up for an average of 4 years, 82% were 65-74 (3,726) while 18% (806) were 75 and over. Most women (80%) had no prior HRT use. Women treated with 0.625 mg conjugated estrogens, plus 2.5 mg medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Ninety percent of cases of probable dementia occurred in the 54% of women that were older than 70.

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

Paediatric use
No data available.

Effects on laboratory tests
No data available.

4.5 Interaction with Other Medicines and Other Form of Interactions

The metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes such as

barbiturates (e.g. phenobarbital), anticonvulsants (e.g. 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 estrogens.

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

4.6 Fertility, Pregnancy and Lactation

Effects on fertility
No data available.

Use in pregnancy
Category D. Known or suspected pregnancy is a contraindication to Estrofem therapy.

Use in lactation
Estrofem is not indicated during lactation.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (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 in Table 1 may occur during Estrofem treatment.

Table 1

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		Migraine
Eye disorders			Vision abnormal NOS.	
Vascular disorders			Venous embolism NOS	Venous thrombosis
Gastrointestinal disorders		Abdominal pain or nausea	Dyspepsia, vomiting, flatulence or bloating	
Hepatobiliary disorders			Cholelithiasis	
Skin and subcutaneous tissue disorders		Skin reactions	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		
Respiratory, thoracic and mediastinal disorders				Asthma

Breast cancer, thromboembolic disorders, as well as changes in hepatic function, have been reported.

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 estrogen 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
- Estrogen-dependent neoplasms benign and malignant. e.g. endometrial cancer (see 'Section 4.4 Special Warnings and Precautions for Use'), endometrial hyperplasia or increase in size of uterine fibroids*
- Insomnia
- Epilepsy
- Libido disorder NOS (not otherwise specified)
- Deterioration of asthma
- Probable dementia (see 'Section 5.1 Pharmacodynamic Properties' – 'Clinical trials')

* In non-hysterectomised woman

Breast cancer risk
The level of risk is dependent on the duration of use (see 'Section 4.4 Special Warnings and Precautions for Use').

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

Table 2 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 starting 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' use**
Estrogen-only HRT			
50	13.3	1.2	2.7
Combined estrogen-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.			

Table 3 Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m²)

Age at starting HRT (years)	**Incidence per 1,000 never users of HRT over a 10 year period (50-59 years)***	**Risk ratio**	**Additional cases per 1,000 HRT users after 10 years**
Estrogen-only HRT			
50	26.6	1.3	7.1
Combined estrogen-progestagen			
50	26.6	1.8	20.8
* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m²). Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

Table 4 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 estrogen-only			
50-79	21	0.8 (0.7-1.0)	-4 (-6-0)*
CEE+MPA estrogen-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 estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see 'Section 4.4 Special Warnings and Precautions for Use'). Depending on the duration of estrogen-only use and estrogen 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. The appropriate addition of a progestagen to an estrogen regimen lowers this additional 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 estrogen-only or combined estrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see 'Section 4.4 Special Warnings and Precautions for Use'). 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 Special Warnings and Precautions for Use'). Results of the WHI studies are presented below.

Table 5 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 estrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)
Oral combined estrogen-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 estrogen progestagen HRT over the age of 60 (see 'Section 4.4 Special Warnings and Precautions for Use').

Risk of ischaemic stroke
The use of estrogen-only and estrogen-progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. 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 Special Warnings and Precautions for Use').

Table 6 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 suspected adverse effects
Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action
The pharmacological actions of exogenous estradiol are similar to the physiological effects of the endogenous hormone. The 17β-estradiol in Estrofem is chemically and biologically identical to endogenous human estradiol and is therefore classified as a human estrogen.

Estrofem restores plasma estrogen levels and thus relieves or decreases estrogen deficiency symptoms. Estrofem suppresses gonadotrophin secretion (FSH/LH) and improves vaginal cytology in post-menopausal women. Estrofem has a positive effect on the symptoms of the urogenital estrogen deficiency syndrome including lower urinary tract dysfunction and atrophic vaginitis. Estradiol is known to decrease LDL-C and increase HDL-C and triglycerides.

Clinical trials

WHI study[(1)]
In a prospective randomised trial (Women's Health Initiative, WHI) involving 8506 postmenopausal women who received oral hormone replacement therapy (HRT) using a continuous combined regimen of conjugated equine estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day and 8102 women who received placebo for an average of 5.2 years, adverse effects on cardiovascular disease and breast cancer, and beneficial effects on hip and total fractures and colorectal cancer were observed. These results do not necessarily apply to lower dosages of these drugs, to other formulations of oral estrogens and progestins, or to estrogen monotherapy.

The WHI study was designed to investigate the efficacy and safety of long-term HRT in preventing coronary heart disease (CHD) in healthy postmenopausal women with an intact uterus. 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.

After a mean of 5.2 years of follow up, the study was prematurely stopped because the risk-benefit profile was not consistent with the requirements for a viable intervention for primary prevention of chronic diseases.

Table 7: 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 8: 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

Million Women study[2]

The results of the cohort study (see Table 3) were based on the follow up on one million, eighty-four thousand, one hundred and ten (1,084,110) women. The average age of the women at recruitment was 55.9 years and the average period of follow up was 2.6 years for analyses of the cancer incidence and 4.1 years for analyses of mortality; the average duration of treatment was over 6 years. Overall, 50% of the study population had used HRT at some point. There were nine thousand, three hundred and sixty four (9,364) newly diagnosed cases of invasive breast cancer and six hundred and thirty seven (637) deaths from breast cancers. The current users of HRT at recruitment were more likely to be diagnosed with breast cancer and to die from it. Past users of HRT were not at an increased risk of newly diagnosed or fatal disease. The incidence was significantly increased for current users of preparations containing estrogen only, estrogen/progestagen and tibolone but the magnitude of the associated risk was greater for the combined treatment than for any other preparation.

Table 9: Relative risk of newly diagnosed invasive breast cancer in relation to recency and type of HRT used

HRT use at baseline	*Cases / population*	*Relative risk (95% FCI)**
All never users	2894/392,757	1.00 (0.96-1.04)
All past users	1044/150,179	1.01 (0.95-1.08)
Current users of:		
Estrogen only	991/115,383	1.30 (1.22-1.38)
Estrogen-progestagen	1934/142,870	2.00 (1.91-2.09)
Tibolone	184/18,186	1.45 (1.25-1.67)
Other/unknown types	93/9,548	1.44 (1.17-1.76)

FCI=floated CI. *Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region and deprivation index.
Modified from Lancet 2003; 362:421

An important finding of the Million Women study was that the relative risks of breast cancer were increased separately from oral, transdermal and implanted estrogen only formulations.

In terms of absolute risk, after ten years' use of HRT, it is estimated that there would be 5 (95% CI 3-7) additional breast cancers per 1,000 users of estrogen only preparations and 19 (95% CI 15-23) additional cancers per 1,000 users of estrogen/progestagen combinations. The elevated risk reduces after discontinuation of hormone replacement therapy and is effectively lost after 5 years.

In the combined HRT subset of WHI, a 26% increase of invasive breast cancer (38 versus 30 per 10,000 person years) after an average of 5.2 years treatment was observed in women receiving the estrogen/progestagen combination compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on study medication. Women reporting prior postmenopausal hormone use had a higher relative risk for breast cancer associated with HRT than those who never used postmenopausal hormones.

In the estrogen-only subset of WHI[3], no increase in breast cancer incidence in hysterectomised postmenopausal women treated with conjugated equine estrogen alone was observed. After a mean (SD) follow-up of 7.1 (1.6) years, the invasive breast cancer hazard ratio (HR) for women assigned to CEE vs placebo was 0.80 (95% confidence interval [CI], 0.62-1.04; P=.09) with annualised rates of 0.28% (104 cases in the CEE group) and 0.34% (133 cases in the placebo group). In exploratory analyses, ductal carcinomas (HR, 0.71; 95% CI, 0.52-0.99) were reduced in the CEE group vs placebo group; however, the test for interaction by tumour type was not significant (P=.054).

WHIMS sub-study[4]
In a study of women 65 years of age and older (a randomised controlled sub-study of the Women's Health Initiative, the Women's Health Initiative Memory Study; n = 4,532, 54% older than 70), those treated with 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. After an average follow-up of 4 years, the absolute risk of probable dementia was 45 per 10,000 women-years in the estrogen plus progestagen group and 22 per 10,000 women-years in the placebo group. It is unknown whether these findings apply to younger postmenopausal women. It is unlikely that HRT would be indicated in this age group.

5.2 Pharmacokinetic Properties

Micronised estradiol is rapidly and efficiently absorbed from the gastrointestinal tract following oral administration. Peak plasma concentrations of estradiol occur 4-6 hours after tablet ingestion. Thereafter elimination is slow and estradiol levels are maintained above baseline for 24 hours. The steady state plasma level of estradiol ranges between 70-100 pg/mL. Estradiol has a half-life of approximately 14-16 hours. In the bloodstream more than 90% of estradiol is bound to plasma proteins. Some estradiol is converted to estrone in the intestinal mucosa before absorption into the portal vein. During passage through the liver a significant proportion of estradiol is metabolised to estrone. Estriol and hydroxyestrones are also produced as well as sulfate and glucuronate conjugates. Circulating estrone sulfate may be reconverted to estrone and estradiol in extrahepatic organs like the uterus. Estrogens are excreted into the bile and undergo significant enterohepatic cycling. Biologically inactive glucuronide and sulfate conjugates are excreted in the urine (90 to 95%) and unconjugated estrogen metabolites appear in the faeces (5 to 10%). Estrogens are also secreted in the milk of nursing mothers.

5.3 Preclinical Safety Data

Genotoxicity

There is limited evidence available in the literature suggesting that estradiol may be weakly genotoxic. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy and an increased incidence of sister chromatid exchanges (indicative of DNA damage) in mammalian cells. None of these effects were induced by estradiol in human lymphocyte cultures. Importantly, there was no evidence of clastogenicity in rodent bone marrow micronucleus assays.

Carcinogenicity

Supra-physiological doses of estradiol have been associated with the induction of tumours in estrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose monohydrate, maize starch, hyprolose, purified talc, magnesium stearate, hypromellose, titanium dioxide, propylene glycol (red 1 mg tablets only), Macrogol 400 (blue 2 mg tablets only), iron oxide red; indigo carmine.

Estrofem does not contain clinically significant amounts of gluten.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Store Estrofem in a dry place, protected from light. Store below 25°C. Do not refrigerate. Keep out of reach of children.

6.5 Nature and Contents of Container

Estrofem is supplied in a calendar dial pack containing 28 tablets.

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of by takin it to your local pharmacy.

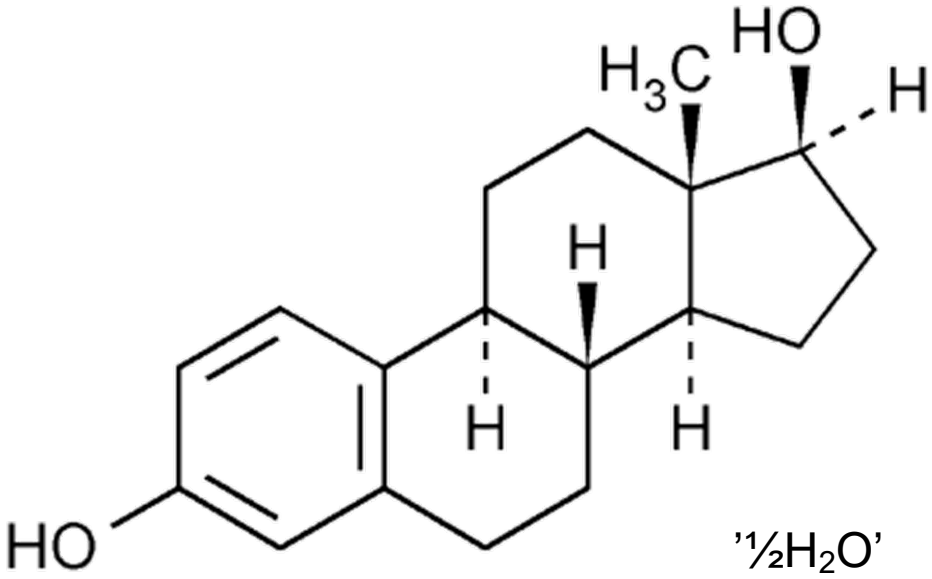
6.7 Physicochemical Properties

Estradiol is a white or almost white crystalline powder which is practically insoluble in water and soluble in acetone.

Chemical structure

Active ingredients: estradiol - chemical name: estra-1,3,5(10)-triene-3,17β-diol (as hemihydrate). Estradiol has 5 chiral centres. The molecular formula is $C_{18}H_{24}O_2$.

Estradiol hemihydrate has a molecular weight of 281.39.



CAS number

35380-71-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Only Medicine

8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Ltd
Level 10, 118 Mount Street
North Sydney NSW 2060

9. DATE OF FIRST APPROVAL

17 November 2011

10. DATE OF REVISION

23 September 2021

REFERENCES

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(3) Stefanick ML, Anderson GL *et al*, for the WHI Investigators. JAMA 2006; 295:1647-1657
(4) Shumaker SA, Legault C, *et al*. JAMA 2003; 289:2651-2662
(5) Scarabin P-Y, Oger E, *et al*. Lancet 2003; 362:428-432
(6) Grodstein F, Manson JE, *et al*. Ann Intern Med 2000; 133; 933-941

Summary table of changes

Section changed	Summary of new information
All	PI Reformat
4.4 and 4.8	Updated with new information on the known risks of breast cancer