AUSTRALIAN PRODUCT INFORMATION
Estrogel® (estradiol hemihydrate) gel

1 NAME OF THE MEDICINE

Estradiol hemihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Estrogel contains the active ingredient estradiol (as hemihydrate). One gram of gel contains 0.6 mg (0.06% w/w) estradiol.

Each pump actuation delivers 1.25 g of gel which contains 0.75 mg of estradiol.

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Estrogel transdermal gel is a clear, colourless gel with an odour of alcohol.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women.
- Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. (see also Section 4.4 Special warnings and precautions for use)

The experience treating women older than 65 years is limited. The lowest effective dose should be used for the shortest duration (see Sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Estrogel as an estrogen only product is indicated only for women without a uterus. Estrogel should be administered daily on a continuous basis.

In women with an intact uterus it is recommended to add a progestogen (e.g. progesterone) for at least 12 days of each month, in accordance with the manufacturers' recommendations.

Menopausal symptoms:

Each metered dose (1 pump actuation) from the dispenser is 1.25 g of Estrogel. Although some women will respond to 1.25 g daily, the most usual starting dose is two pumps (2.5 g which contains 1.5 mg estradiol) of Estrogel once daily. In the majority of women this dose will provide

effective relief of menopausal symptoms. If after one month's treatment effective relief is not obtained, the dosage may be increased to three or to a maximum of four pumps (5 g which contains 3.0 mg estradiol) of Estrogel daily.

The lowest effective dose should be used for maintenance therapy. The optimal daily maintenance dose needs to be reevaluated on a regular (e.g. annually) basis. Estrogel should only be continued for as long as the benefit outweighs the risk.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose should be used for the shortest duration (see also section 4.4 Special warnings and precautions for use).

Long-term safety of daily doses of Estrogel above 2.5 g (1.5 mg estradiol) has not been established.

Prevention of osteoporosis:
The minimum effective dose is 2.5 g of Estrogel once daily for most patients. Use with progestogen:

In women with an intact uterus the recommended dose of a progestogen should be administered for at least 12 days of each month, in accordance with the manufacturers' recommendations. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

Initiation of treatment:

Women who are post-menopausal or have very infrequent menstrual cycles:

Treatment with Estrogel can be started on any day.

Switching from a continuous estrogen-progestogen combined HRT:

Treatment with Estrogel can be started on any day of the cycle.

Switching from a cyclic or continuous sequential HRT treatment:

Finish the therapeutic sequence before beginning treatment with Estrogel.

Method of Administration

The pump pack will require priming before using a new pump pack for the first time. The first dose dispensed should be discarded.

The correct dose of gel should be dispensed and applied to clean, dry, intact areas of skin e.g. on the arms and shoulders, and/or inner thighs. The area of application should be as large as possible.

For low dose Estrogel (1 pump), Estrogel should be applied to both top and bottom of one arm from the shoulder to the wrist.

For standard dose Estrogel (2 pumps), 1 pump should be applied to both top and bottom of one

arm from shoulder to wrist. The second dose is applied the same way to the other arm.

For a higher dose of Estrogel, 2 pumps of Estrogel should be applied to both top and bottom of one arm from shoulder to wrist. The third dose (1 pump) is applied the same way to the other arm. The inner thigh can also be used.

For the highest approved dose (4 pumps), 2 pumps of Estrogel should be applied to both the top and bottom of one arm from shoulder to wrist. The 2 additional doses (2 pumps) are applied the same way to the other arm. The inner thigh can also be used.

Estrogel Dose	Application Area
1 Pump	1 pump should be applied to both top and bottom of one arm from the shoulder to the wrist.
2 Pumps	1 pump should be applied to both top and bottom of one arm from shoulder to wrist. The second dose (1 pump) is applied the same way to the other arm.
3 Pumps	2 pumps of Estrogel should be applied to both top and bottom of one arm from shoulder to wrist. The third dose (1 pump) is applied the same way to the other arm. The inner thigh can also be used.
4 Pumps	2 pumps of Estrogel should be applied to both the top and bottom of one arm from shoulder to wrist. 2 additional doses (2 pumps) are applied the same way to the other arm. The inner thigh can also be used.

Estrogel should NOT be applied on or near the breasts or on the vulval region.

Estrogel should be allowed to dry for 5 minutes before covering the skin with clothing.

The gel should be applied by the patient herself, not by anyone else, and skin contact, particularly with a male partner, should be avoided for one hour after application. Wash hands with soap and water after applying the gel. Washing the skin or contact with other skin products should be avoided until at least one hour after application of Estrogel.

For people not being treated with Estrogel:
In the event of contact with an application area, which has not been washed or is not covered with clothing, wash the area of skin onto which Estrogel may have been transferred as soon as possible, using soap and water.

If the patient forgets to apply a dose and it is more than 12 hours until the next dose, the missed dose should be applied and normal dosing resumed the next day. If the next dose is less than 12 hours away, it is best just to wait and apply the next dose normally. Patients should be advised not to apply two doses at the same time.

Forgetting a dose may increase the likelihood of break-through bleeding and spotting.

Method of Administration
For transdermal use.

4.3 CONTRAINDICATIONS

- Known, past or suspected breast cancer;
- Known or suspected estrogen-dependent malignant tumours (*e.g.* endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous or current venous thromboembolism (*e.g.* 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 as long as liver function tests have failed to return to normal;
- Known or suspected pregnancy;
- Lactation;
- Known hypersensitivity to the active substances or to any of the excipients;
- Porphyria

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually, and HRT should only be continued as long as the benefit outweighs the risk.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical Examination and Follow-Up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by 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, 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 Estrogel, 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
- Liver disorders (*e.g.* liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus (SLE)
- 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 and in the following situations:

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

Endometrial hyperplasia and carcinoma

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and estrogen dose (see section 4.8 Adverse effects (Undesirable effects)). After stopping treatment risk may remain elevated for at least 10 years.

- The addition of a progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined estrogen-progestogen therapy in non- hysterectomised women prevents the excess risk associated with estrogen-only HRT.

- Break-through bleeding and spotting may occur during the first months of treatment. If break-through 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 progestogens to estrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis if they are known to have residual endometriosis.

Breast cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined estrogen-progestogen and possibly also estrogen-only HRT, that is dependent on the duration of taking HRT.

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 substantially lower than that found in users of estrogen-progestogen combinations (see section 4.8 Adverse effects (Undesirable effects)).

Combined estrogen-progestogen therapy

The randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and 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 years (see Section 4.8 Adverse effects (Undesirable effects)).

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

HRT, especially estrogen-progestogen 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 estrogen-only or combined estrogen-progestogen 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)).

Venous thromboembolism

- HRT is associated with a 1.3 – 3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8 Adverse effects (Undesirable effects)).
- 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, 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 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 historyof VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counseling 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).

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 estrogen- progestogen or estrogen-only HRT.

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

Combined estrogen-progestogen therapy:
The relative risk of CAD during use of combined estrogen+progestogen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to estrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Ischaemic Stroke

Combined estrogen-progestogen and estrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischemic 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)).

Other conditions

Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

- Women with pre-existing hypertriglyceridaemia 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.

Effects on thyroid function

Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid-replacement therapy. These women should have their thyroid function monitored in order to maintain an acceptable range.

Use in the elderly

The experience treating women older than 65 years is limited.

HRT use does not improve cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.

Paediatric Use

Use in children is not recommended.

There is limited data available supporting the use of transdermal estradiol in paediatric indications such as Turners Syndrome and Pubertal Induction. The treating physician should determine the benefits and risks of use of Estrogel in children prior to initiating treatment.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Treatment with surface active agents (*e.g.* sodium lauryl sulphate), or other drugs which alter barrier structure or function, could remove drug bound to the skin, altering transdermal flux. Therefore, patients should avoid the use of strong skin cleansers and detergents (*e.g.* benzalkonium or benzothonium chloride products), skin care products of high alcoholic content (astringents, sunscreens) and keratolytics (*e.g.* salicylic acid, lactic acid).

The use of any concomitant skin medication which alters skin production (*e.g.* cytotoxic drugs) should be avoided at the site of application of Estrogel.

Sun exposure and photo-irritation
Estrogel did not exhibit reactions that were indication of photo-irritation or photoallergy. Estrogel was well tolerated by the subjects with no clinically relevant findings.

The metabolism of estrogens 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, carbamezapine) 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.

At transdermal administration, the first-pass effect in the liver is avoided and thus, transdermally applied estrogens HRT might be less affected than oral hormones by enzyme inducers.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
No specific studies on fertility have been conducted with Estrogel. Estradiol has been shown to impair fertility in animals.

Use in pregnancy (Category B3)
Estrogel must not be used during pregnancy (see CONTRAINDICATIONS). If pregnancy occurs during medication with Estrogel, treatments should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to estrogens indicate no teratogenic or fetotoxic effects.

Use in lactation
Estrogel must not be used during breast-feeding (see CONTRAINDICATIONS). Estradiol is excreted in human breast milk.

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)

Summary of the safety profile
The undesirable effects are generally mild and rarely require treatment withdrawal. Undesirable effects, if any, usually occur during the first months of treatment.

Undesirable effects observed with HRT products used in menopause are reported in the Table 1 below:

Adverse reactions were categorised as very common (≥ 1/10), common (≥ 1/100 to ≤ 1/10), uncommon (≥ 1/1,000 to ≤ 1/100) or rare (≥ 1/10,000 to ≤ 1/1,000).

Table 1: Undesirable effects observed in HRT products used in menopause

System Organ Class	Frequency of occurrence of adverse reactions		
	Common	Uncommon	Rare
Metabolism and nutrition disorders			Glucose intolerance
Psychiatric disorders		Depression Mood swings	Change in libido
Nervous system disorders	Headache,	Vertigo Migraine	Aggravation of epilepsy
Vascular disorders		Venous thromboembolic disease	Arterial hypertension
Gastrointestinal disorders	Nausea Abdominal pain	Flatulence Vomiting	
Hepato- biliary disorders			Liver function tests abnormalities
Skin and subcutaneous tissue disorders		Pruritus	Skin decoloration Acne
Reproductive system and breast disorders	Breast swelling/pain Breast enlargement Dysmenorrhoea Menorrhagia, Metrorraghia Leucorrohoea Endometrial hyperplasia	Benign breast neoplasm Increased volume of uterine leiomyoma Vaginitis/vaginal candidiosis	Galactorrhea
General disorders and administration site condition	Weight change (increase or decrease) Water retention with peripheral oedema	Asthenia	Anaphylactic reaction (in women with past history of allergic reaction)

Other adverse reactions have been reported in association with estrogen/progestogen treatment:
- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see Section 4.4 Special warnings and precautions for use).

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking

combined estrogen-progestogen therapy for more than 5 years.
- Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see Section 4.4 Special warnings and precautions for use).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented Table 2 and Table 3 below.

Table 2: Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period[2]	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
		Estrogen only HRT	
50-65	9-12	1.2	1-2 (0-3)
		Combined estrogen-progestogen	
50-65	9-12	1.7	6 (5-7)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

[2] Taken from baseline incidence rates in developed countries

Table 3: US WHI studies - additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
		CEE estrogen only	
50-79	21	0.8 (0.7-1.0)	-4 (-6 – 0) [3]
		CEE +MPA estrogen-progestogen‡	
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

‡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.

[3] WHI study in women with no uterus, which did not show an increase in risk of breast cancer

Endometrial cancer risk

Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1000 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 epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestogen to estrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Use of estrogen-only or combined estrogen-progestogen 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 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-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 HT (see section 4.4 Special warnings and precautions for use). Results of the WHI studies are presented in Table 4:

Table 4: WHI studies combined - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only[4]			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined estrogen-progestogen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 – 13)

[4]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-progestogen 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 + progestogen 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 as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age refer Table 5, see section 4.4 Special warnings and precautions for use.

Table 5: WHI studies combined - Additional risk of ischaemic stroke[5] over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1– 1.6)	3 (1 – 5)

[5]*no differentiation was made between ischaemic and haemorrhagic stroke.*

Reporting of suspected adverse reactions
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 www.tga.gov.au/reporting-problems

4.9 OVERDOSE

Pain in the breasts or excessive production of cervical mucus may be indicative of too high a dosage, but acute overdosage has not been reported and is unlikely to be a problem. Overdosages of estrogen may cause nausea, and withdrawal bleeding may occur. There are no specific antidotes and treatment should be symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC Code: G03CA03.
Sex Hormones and Modulators of the Genital System - Natural and Semisynthetic Estrogens, plain.

Mechanism of action
The active ingredient, estradiol, is chemically and biologically identical to endogenous human estradiol, the major and most potent estrogenic hormone secreted by the ovary from menarche to

menopause. Estrogens are important for the development and maintenance of the female reproductive system and secondary sexual characteristics, and modulate various physiological processes, including bone resorption. Exogenous estradiol substitutes for the loss of endogenous estrogen production in menopausal women to alleviate menopausal symptoms, and prevents bone loss following menopause or ovariectomy.
Clinical trials

Estrogen Deficiency Symptoms

Estrogen supplementation is recognised as an effective treatment for reducing the frequency and severity of hot flushes. A Cochrane review estimated that oral HRT reduces the frequency of hot flushes by 75% and eases severity (MacLennan 2004), a subsequent meta-analysis showed that oral estradiol resulted in 16.8 fewer hot flushes per week (Nelson 2004). Estrogen with or without progesterone is recommended for management of vasomotor menopausal symptoms by HRT guidelines worldwide (Santen 2010,Sturdee 2011,Panay 2013,de Villiers 2016); the Global Consensus Statement on menopausal hormone therapy specifies HRT as the most effective treatment for vasomotor symptoms (de Villiers 2016).

Efficacy data for Estrogel in the treatment of estrogen deficiency symptoms in postmenopausal women was provided by 9 company sponsored studies (Archer 2003, CV141-002 1999, Archer 2012, Foidart 1994, Kornafel 1992, Christiansen 1988, Jensen 1987b, Dupont 1991, Sentrakul 1991) and 11 non-company sponsored studies (Mizunuma 2011, Akhila 2006, Foidart 1997, Pelissier 1999 and Pelissier 2001, Faguer de Moustier 1989, Holst 1987, Holst 1983a, Vihtamaki 1998, Elkik 1982, Polo-Kantola 1999, Basdevant 1991).

Compared with placebo, Estrogel produced a significantly greater decrease in the frequency and severity of hot flushes (Archer 2012 (0.75-1.5 mg estradiol), Archer 2003 (0.75-1.5 mg estradiol), Kornafel 1992 (1.5 mg estradiol), Christiansen 1988 (3 mg estradiol), Polo- Kantola 1999 (1.5 mg estradiol)); a larger decrease with Estrogel versus placebo was also reported by Jensen 1987b (3 mg estradiol) although a statistical analysis was not reported. Mizunuma 2011 showed that, after an induction phase in which Estrogel decreased the incidence of hot flushes (1.08 mg estradiol), subjects who switched to placebo saw an increase in the incidence of hot flushes back to baseline levels (0.54 mg estradiol maintenance phase). Estrogel also significantly improved vaginal atrophy markers when compared with placebo (Archer 2012 (0.75-1.5 mg estradiol), Archer 2003 (0.75-1.5 mg estradiol), Kornafel 1992 (1.5 mg estradiol)).

Estrogel efficacy in the relief of menopausal symptoms was not significantly different from estradiol transdermal patches (Akhila 2006 (1.5 mg estradiol), Foidart 1997 (1.5 mg estradiol)).

When compared with other transdermal regimens, the efficacy of Estrogel at a dose of 1.5 mg/day in the relief of menopausal symptoms was not significantly different from estradiol transdermal patches (CV141-002 1999 (0.375-1.5 mg estradiol), Akhila 2006 (1.5 mg estradiol), Foidart 1997 (1.5 mg estradiol)), although the lower 0.75 mg/day Estrogel dose was not as effective as a 50 µg/day transdermal patch (CV141-002 1999). When compared with oral estrogen regimens, Akhila 2006 determined Estrogel (1.5 mg estradiol) efficacy to be significantly better than oral conjugated estrogen when assessed by the incidence of complete relief of vasomotor symptoms, psychological disturbances, genital symptoms, and urinary symptoms. However, other studies reported that improvements in symptoms were similar with Estrogel and oral regimens (Jensen 1987b, Dupont 1991, Sentrakul 1991, Faguer de Moustier 1989, Elkik 1982, Basdevant 1991).

Improvements in vaginal atrophy markers were also similar between Estrogel (1.5 mg estradiol) and oral regimens (0.625 mg conjugated estrogens) (Dupont 1991). One Estrogel study noted potential efficacy of Estrogel in managing insomnia (Dupont 1991).

Where reported, the addition of oral progesterone did not alter the Estrogel response.
In the 4-year KEEPS study, recently postmenopausal women had similar and substantial reductions in hot flashes and night sweats with lower-than-conventional doses of oral (0.45 mg conjugated estrogens) or transdermal patch estrogen (50 µg/daily). These reductions were sustained during 4 years. Insomnia was intermittently reduced compared with placebo for both hormone regimens (Santoro 2017). A comparison, performed by the company, of data from 2 Estrogel company-sponsored studies (Archer 2012 (0.75-1.5 mg estradiol), Brennan 2001 (0.375-1.5 mg estradiol)) against data from the KEEPS study showed Estrogel to be equivalent to the Climara® patch in the alleviation of hot flushes and similar in systemic estradiol exposure (Piette 2014)

Overall, there is strong support for the efficacy of Estrogel in the treatment of menopausal symptoms.

Prevention of osteoporosis

Estrogen supplementation prevents the usual accelerated increase in bone loss if HRT is started early in menopause, while starting estrogen treatment later stops and to a degree reverses bone loss (Santen 2010), preserves and increases bone mineral density (Santen 2010), and reduces fracture risk by up to 27% (Christenson 2012). In the KEEPS study, both oral and transdermal HRT groups showed favourable effects on bone mineral density compared to the placebo group (Cobin 2017). The Global Consensus Statement on menopausal hormone therapy (de Villiers 2016) and most international guidelines (NICE 2015, Stuenkel 2016, Baber 2016, NAMS 2017, Cobin 2017) state that HRT has been shown to significantly lower the risk of hip, vertebral, and other osteoporosis-related fractures in postmenopausal women.

Efficacy data for Estrogel for the prevention of osteoporosis in postmenopausal women was provided by 3 company-sponsored studies (Jensen 1988 and Johansen 1988, Riis 1987a, Riis 1987b) and 8 non-company sponsored studies (Ng 1993, Yang 2007, Sun 2002, Devogelaer 1998, Wimalawansa 1995, Palacios 1995, Ribot 1990, Tremollieres 1990). Bone mineral content and density remained steady or increased during Estrogel (3 mg estradiol) treatment but decreased during placebo treatment, resulting in significantly higher bone mineral content and density in Estrogel-treated subjects versus placebo-treated subjects (Jensen 1988, Riis 1987a, Riis 1987b). One study showed no change in bone mineral density with either Estrogel or placebo (Ng 1993); however, the study was of shorter duration than the company-sponsored studies (1 year versus 2 years) and used a lower dose of Estrogel (0.75-1.5 mg/day versus 3 mg/day of estradiol).

No studies were identified that compared Estrogel with other transdermal regimens in the prevention of osteoporosis.

When compared with oral regimens, improvements in bone mineral content and density were similar between Estrogel (3mg estradiol) and oral estradiol valerate (2mg estradiol valerate) (Jensen 1988, Riis 1987b), oral conjugated estradiol (0.625mg/day) (Palacios 1994), and oral intermittent cyclically-administered etidronate (400mg/day) (Wimalawansa 1995). The improvement in bone mineral density with Estrogel dose range (0.75-1.5 mg estradiol) was

significantly greater than with oral estriol (2 mg/day) (Yang 2007, Devogelaer 1998).

The remaining study, which compared Estrogel doses, also supported the efficacy of Estrogel in preventing the postmenopausal decline in bone mineral density when administered at doses of 1.5 mg/day of estradiol or above (Sun 2002).
Where reported, the addition of oral progesterone did not alter the Estrogel response.

Overall, the efficacy studies strongly support the efficacy of Estrogel in the prevention of postmenopausal osteoporosis.

In summary, the efficacy of Estrogel in the treatment of estrogen deficiency symptoms has been demonstrated for treatment durations of up to 2 years (Christiansen 1988 and Jensen 1987b) and the effect of Estrogel on osteoporosis has been demonstrated for up to 4 years (Sun 2002). No evidence of tolerance to the efficacious effects of Estrogel was reported.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Pharmacokinetic studies indicate that, when applied topically to a large area of skin in a volatile solvent, approximately 10% of the estradiol is percutaneously absorbed into the vascular system, regardless of the age of the patient. Daily application of 2.5 g or 5 g Estrogel over a surface area of 400- 750 cm^2 results in a gradual increase in estrogen blood levels to steady state after approximately 3-5 days and provides circulating levels of both estradiol and estrone equivalent in absolute concentrations and in their respective ratio to those obtained during the early-mid follicular phase of the menstrual cycle.

Estrogel was administered to 17 postmenopausal women once daily on the posterior surface of one arm from wrist to shoulder for 14 consecutive days. Maximum serum concentrations (C_{max}) of estradiol and estrone on Day 12 were 117 pg/ml and 128 pg/ml, respectively.

The time-averaged serum estradiol and estrone concentrations ($C_{average}$) over the 24 hour dose interval after administration of 2.5 g of Estrogel on Day 12 were 76.8 pg/ml and 95.7 pg/ml, respectively.

When treatment is stopped, estradiol and urinary conjugated estradiol concentrations return to baseline in about 76 hours.

Distribution

Estradiol is extensively bound to plasma proteins, mainly to sex hormone binding globulin (SHBG) and to a lesser degree albumin. Only around 2% is free and biologically active. Tissue distribution of unbound estradiol is rapid and wide.

Metabolism

Once systemically absorbed, transdermally applied estradiol is metabolised in the same way as the endogenous hormone. Estradiol is metabolised primarily in the liver to estrone, then later to estriol, epioestriol and catechol estrogens, which are then conjugated to sulfates and glucuronides. Metabolism involves multiple CYP isozymes, but is predominantly mediated by CYP3A4. Estriol

is glucuronidated by UGT1A1. Estradiol metabolites are subject to enterohepatic circulation.

Excretion

Excretion is mainly via the urine (as conjugated metabolites). Only a small amount is excreted in faeces.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Estradiol shows some genotoxic activity *in vitro*. While mutagenicity was not observed with estradiol in bacterial cells (Ames test), positive results have been obtained with the compound in assays for mutagenicity, induction of chromosomal aberrations, aneuploidy, sister chromatid exchange (indicative of DNA damage), and single-strand DNA breaks in mammalian cells. No clastogenicity was observed with estradiol *in vivo* in rodent bone marrow micronucleus assays. Reactive catechol metabolites of estradiol have been found to form DNA adducts.

Carcinogenicity

Long-term, continuous administration of natural and synthetic estrogens in laboratory animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. Carcinogenicity by estradiol may involve gene mutation induced by reactive metabolites or the activation of estrogen receptor-mediated signaling pathways that sustain the growth and survival of preneoplastic and malignant cells.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

-Ethanol

-Carbomer 980

-Trolamine

-Purified water

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 below 30ºC. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

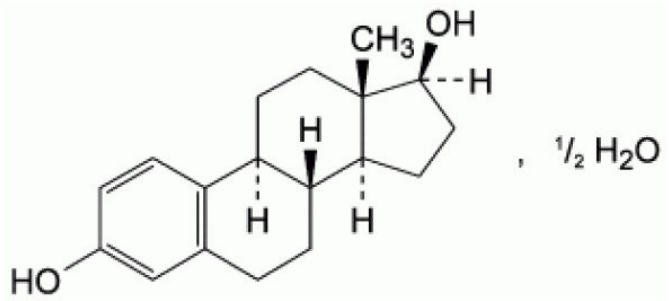
Metering canister composed of a polypropylene bottle, a LDPE pouch, a polypropylene metering pump and closed with a polypropylene cap, containing 80 g of gel and are available in packs of 1, 2 and 3 pump(s).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Estradiol

Molecular formula: $C_{18}H_{24}O_2,½H_2O$

CAS No: 35380-71-3

7 MEDICINE SCHEDULE (POISON STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Besins Healthcare Australia Pty Ltd
Suite 3, Level 2, Tower 1,
495 Victoria Avenue,
Chatswood NSW 2067

For Medical information call 1800 BESINS (1800 237 467)

9 DATE OF FIRST APPROVAL

08 May 2019

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information