AUSTRALIAN PRODUCT INFORMATION – PREMARIN® (conjugated estrogens)

WARNING

Endometrial cancer

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 (see Section 4.4 Special warnings and precautions for use, Malignant neoplasms, Endometrial cancer).

Cardiovascular and other risks

Estrogens with or without progestogens should not be used for the prevention of cardiovascular disease or dementia (see Sections 5.1 Pharmacodynamic properties, Clinical trials and 4.4 Special warnings and precautions for use, Cardiovascular risk and Dementia).

The estrogen-alone substudy of the Women's Health Initiative (WHI) study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with conjugated estrogens (CE 0.625 mg) relative to placebo (see Sections 5.1 Pharmacodynamic properties, Clinical trials and 4.4 Special warnings and precautions for use, Cardiovascular risk).

The estrogen plus progestogen substudy of the WHI reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with conjugated estrogens combined with medroxyprogesterone acetate (CE 0.625 mg/MPA 2.5 mg) relative to placebo (see Sections 5.1 Pharmacodynamic properties, Clinical trials and 4.4 Special warnings and precautions for use, Cardiovascular risk and Malignant neoplasms, Breast cancer).

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with CE alone and during 4 years of treatment with CE/MPA relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (see Sections 5.1 Pharmacodynamic properties, Clinical trials and 4.4 Special warnings and precautions for use, Dementia and Use in the elderly).

Other doses of CE and MPA and other combinations and dosage forms of estrogens and progestogens were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1. NAME OF THE MEDICINE

Conjugated estrogens.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PREMARIN 0.3 mg tablets contain 0.3 mg conjugated estrogens as the active ingredient.

PREMARIN 0.625 mg tablets contain 0.625 mg conjugated estrogens as the active ingredient.

Excipient(s) with known effect

PREMARIN tablets contain sugars (lactose monohydrate, sucrose).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Film coated tablet.

The 0.3 mg tablets are dark green and marked "0.3".

The 0.625 mg tablets are maroon and marked "0.625".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Estrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

PREMARIN is indicated as replacement therapy for estrogen deficiency states associated with climacteric manifested by:

- moderate to severe vasomotor symptoms associated with the estrogen deficiency in natural and surgical menopause (sweating, hot flushes).

Periodic re-evaluation with a view to short term treatment is recommended.

- atrophic vaginitis.

When prescribing solely for the treatment of symptoms of vaginal atrophy, topical vaginal products should be considered.

There is no evidence that estrogens are effective for anxiety or depression without associated vasomotor symptoms and they should not be used to treat such conditions.

PREMARIN is indicated for the prevention of postmenopausal osteoporosis in select patients.

When prescribed solely for the prevention of postmenopausal osteoporosis, therapy should only be prescribed for women who are at high risk of osteoporosis and future fracture and who are intolerant of, or contraindicated for, non-estrogen products approved for prevention of osteoporosis. Life style modifications and the risk benefit profile of PREMARIN should be taken into careful consideration and discussed with the patient, to allow the patient to make an

informed decision prior to prescribing (see Section 4.4 Special warnings and precautions for use and Section 4.2 Dose and method of administration**)**.

Hypoestrogenic states, e.g., female hypogonadism, primary ovarian failure or female castration.

See BOXED WARNING, particularly when considering PREMARIN for long term usage.

4.2 Dose and method of administration

Continuous daily administration of PREMARIN is generally recommended.

Physicians should advise their patients that the tablets should be swallowed whole. The tablets should not be divided, crushed, chewed, or dissolved in the mouth.

Patients should be re-evaluated periodically to determine if treatment for symptoms is still necessary. See the statements in the BOXED WARNING, particularly when considering PREMARIN for long term usage.

For women with an intact uterus, when indicated for climacteric symptoms or prevention of postmenopausal osteoporosis, it is recommended that a progestogen is administered (see Section 4.4 Special warnings and precautions for use, Malignant neoplasms). For continuous PREMARIN administration, a progestogen should be added for at least 10-14 consecutive days each month. In some cases, hysterectomised women with a history of endometriosis may need a progestogen (see Section 4.4 Special warnings and precautions for use, Exacerbation of other conditions). If PREMARIN is administered cyclically (i.e., 21 days out of 28 days), it is recommended that the progestogen is added for the last 10-14 days of the estrogen course.

Climacteric symptoms

For treatment of moderate to severe vasomotor symptoms and atrophic vaginitis associated with the menopause, the lowest dose that will control symptoms should be chosen.

Vasomotor symptoms: 0.3 mg to 1.25 mg daily.

Atrophic vaginitis: 0.3 mg to 1.25 mg daily, depending upon the tissue responses of the individual patient.

Prevention of postmenopausal osteoporosis

0.3mg – 0.625mg daily.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake and when indicated pharmacological therapy. Postmenopausal women require an adequate daily intake of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with sub-optimal dietary intake. Vitamin D supplementation may also be required to ensure adequate daily intake in postmenopausal women.

Hypoestrogenism

Female hypogonadism

2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestogen cyclic regimen with PREMARIN, 2.5 to 7.5 mg daily in divided doses. During the last five days of estrogen therapy, give an oral progestogen. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure

0.3 mg to 1.25 mg daily. Adjust dosage according to severity of symptoms and response of the patient.

4.3 Contraindications

PREMARIN is contraindicated in patients with:

- known or suspected pregnancy
- known, suspected or history of breast cancer
- known or suspected estrogen-dependent neoplasia (e.g., endometrial cancer, endometrial hyperplasia)
- undiagnosed abnormal genital bleeding
- active or history of confirmed venous thromboembolism (such as deep venous thrombosis, pulmonary embolism)
- active or history of arterial thromboembolic disease (e.g., stroke, myocardial infarction)
- severe uncontrolled hypertension
- other undiagnosed breast pathology
- active or chronic liver dysfunction or disease
- known thrombophilic disorders (e.g., protein C, protein S or antithrombin deficiency)
- known or suspected hypersensitivity to CE or any excipients in the tablet.

4.4 Special warnings and precautions for use

The benefits and risks of estrogen therapy must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Estrogen therapy or hormone therapy should not be initiated or continued to prevent cardiovascular disease or dementia.

Physical examination

A complete medical and family history should be obtained prior to initiating or reinstating any estrogen therapy. Pretreatment and subsequent physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs including histological endometrial assessment, when indicated and papanicolaou smear. Before starting treatment pregnancy should be excluded. Periodic checkups and careful benefit/risk evaluations should be undertaken in women treated with estrogen therapy.

Combined estrogen and progestogen therapy

There are additional and/or increased risks that may be associated with the use of combination estrogen-progestogen therapy compared with using estrogen-alone regimens. These include an increased risk of myocardial infarction, pulmonary embolism, invasive breast cancer and ovarian cancer (see Section 5.1 Pharmacodynamic properties, Clinical trials).

Cardiovascular risk

An increased risk of stroke and deep vein thrombosis has been reported with estrogen-alone therapy.

An increased risk of stroke, deep vein thrombosis, pulmonary embolism and myocardial infarction has been reported with estrogen-progestogen therapy.

The physician should be aware of the possibility of thrombotic disorders (including thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism) during estrogen therapy and alert to their earliest manifestations.

Should any of these events occur or be suspected, estrogens with or without progestogens should be discontinued immediately.

Patients who have risk factors for thrombotic disorders should be kept under careful observation.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolaemia and obesity) and/or venous thromboembolism (e.g., personal history or family history of venous thromboembolism, obesity and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the estrogen-alone substudy of the WHI, a statistically significant increased risk of stroke was observed in women receiving CE 0.625 mg daily compared to women receiving placebo (45 vs. 33 per 10,000 women-years). The increase in risk was observed in year one and persisted. Should a stroke occur or be suspected, estrogens should be discontinued immediately (see Section 5.1 Pharmacodynamic properties, Clinical trials).

In the estrogen plus progestogen substudy of the WHI, a statistically significant increased risk of stroke was reported in women receiving CE 0.625 mg/MPA 2.5 mg daily compared to women receiving placebo (31 vs. 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted (see Section 5.1 Pharmacodynamic properties, Clinical trials).

Patients who are at risk of developing migraines with aura may be at risk of ischemic stroke and should be kept under careful observation.

Coronary heart disease

In the estrogen-alone substudy of the WHI, no overall effect on coronary heart disease events (defined as non-fatal myocardial infarction, silent myocardial infarction, or death due to coronary heart disease) was reported in women receiving estrogen alone compared to placebo (see Section 5.1 Pharmacodynamic properties, Clinical trials).

In the estrogen plus progestogen substudy of the WHI, no statistically significant increase of coronary heart disease events was reported in women receiving CE/MPA compared to women receiving placebo (39 vs. 33 per 10,000 women-years). An increase in the relative risk was demonstrated in year one and a trend towards decreasing relative risk was reported in years two through five.

Venous thromboembolism (VTE)

In the estrogen-alone substudy of the WHI study, the risk of VTE (deep vein thrombosis and pulmonary embolism) was reported to be increased for women taking CE (30 vs. 22 per 10,000 women-years) although only the increased risk of deep vein thrombosis reached statistical significance (23 vs. 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first two years. Should a VTE occur or be suspected, estrogens should be discontinued immediately (see Section 5.1 Pharmacodynamic properties, Clinical trials).

In the estrogen plus progestogen substudy of WHI, a statistically significant 2 fold greater rate of VTE was reported in women receiving CE/MPA compared to women receiving placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and PE (18 vs. 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted.

If feasible, estrogens should be discontinued at least four to six weeks before surgery of the type associated with increased risk of thromboembolism or during periods of prolonged immobilisation.

Malignant neoplasms

Breast cancer

Studies involving the use of estrogens by postmenopausal women have reported inconsistent results on the risk of breast cancer. The most important randomised clinical trial providing information about this issue is the WHI. In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow up, CE 0.625 mg daily was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80, 95% nominal confidence interval [nCI] 0.62-1.04) (see Section 5.1 Pharmacodynamic properties, Clinical trials).

In the estrogen plus progestogen substudy, after a mean follow up of 5.6 years, the WHI substudy reported an increased risk of breast cancer. In this substudy, prior use of estrogen alone or estrogen plus progestogen combination hormone therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24 (95% nCI 1.01-1.54) and the absolute risk was 41 vs. 33 cases per 10,000 women-years, for estrogen plus progestogen compared with placebo, respectively. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86 and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for estrogen plus progestogen compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09 and the absolute risk was 40 vs. 36 cases per 10,000 women-years for estrogen plus progestogen compared with placebo.

In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen plus progestogen group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histological subtype, grade and hormone receptor status did not differ between the groups (see Section 5.1 Pharmacodynamic properties, Clinical trials).

Some observational studies have reported an increased risk of breast cancer for estrogen alone therapy after several years of use. The risk increased with duration of use and appeared to return to baseline within approximately five years after stopping treatment (only the observational studies have substantial data on risk after stopping).

The observational Million Women study in Europe reported an increased risk of mortality due to breast cancer among current users of estrogens alone or estrogens plus progestogens compared to never users, while the estrogen plus progestogen substudy of WHI showed no effect on breast cancer mortality with a mean follow up of 5.6 years.

The use of estrogen alone and estrogen plus progestogen has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors and prior mammogram results.

Endometrial cancer

The use of unopposed estrogens in women with an intact uterus has been associated with an increased risk of endometrial cancer (see Exacerbation of other conditions).

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users and appears dependent on duration of treatment and on estrogen dose. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen or estrogen plus progestogen combinations 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 estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestogen to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Addition of a progestogen when a woman has not had a hysterectomy

Studies of the addition of a progestogen for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen, have reported a lower incidence of endometrial hyperplasia than would be induced by estrogen treatment alone.

There are, however, possible risks that may be associated with the use of progestogens with estrogens compared to estrogen alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance (see Section 5.1 Pharmacodynamic properties, Clinical trials, Section 4.4 Special warnings and precuations for use, Combined estrogen and progestogen therapy).

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-progestogen hormone replacement therapy (HRT), which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the WHI trial, suggest that the long-term use of combined HRTs may be associated with a similar or slightly smaller risk.

Dementia

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomised women aged 65 to 79 years was randomised to CE 0.625.mg daily or placebo. In the estrogen plus progestogen WHIMS substudy, a population of 4,532 postmenopausal women aged 65 to 79 years was randomised to CE 0.625 mg/MPA 2.5 mg daily or placebo.

In the estrogen-alone substudy, after an average follow up of 5.2 years, 28 women in the estrogen alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone vs. placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for CE alone vs. placebo was 37 vs. 25 cases per 10,000 women-years (see Section 5.1 Pharmacodynamic properties, Clinical trials).

In the estrogen plus progestogen substudy, after an average follow up of four years, 40 women in the estrogen plus progestogen group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestogen vs. placebo was 2.05 (95% CI 1.21-3.48). The absolute risk of probable dementia for CE/MPA vs. placebo was 45 vs. 22 cases per 10,000 women-years (see Section 5.1 Pharmacodynamic properties, Clinical trials).

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women (see BOXED WARNING and Section 4.4 Special warnings and precautions for use, Use in the elderly).

Gallbladder disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Uterine bleeding

Certain patients may develop abnormal uterine bleeding (see Endometrial cancer).

Fluid retention

Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Exacerbation of other conditions

Estrogen therapy may cause an exacerbation of asthma, epilepsy, migraine with or without aura, diabetes mellitus, otosclerosis, porphyria, systemic lupus erythematosus and hepatic haemangioma and should be used with caution in women with these conditions.

Endometriosis may be exacerbated with administration of estrogen therapy. Malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestogen should be considered.

Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomised, placebo controlled clinical trial, a generalised effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals during estrogen use.

Use in hepatic impairment

Estrogens may be poorly metabolised in patients with impaired liver function (see Section 4.3 Contraindications).

History of cholestatic jaundice

For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

Hypercalcaemia

Estrogen administration may lead to severe hypercalcaemia in patients with breast cancer and bone metastases. If hypercalcaemia occurs, use of the medication should be stopped and appropriate measures taken to reduce the serum calcium level.

Hypocalcaemia

Estrogens should be used with caution in patients with severe hypocalcaemia.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are receiving estrogens may require increased doses of their thyroid hormone replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Visual abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilloedema or retinal vascular lesions, estrogens should be discontinued.

Hypertriglyceridaemia

In patients with pre-existing hypertriglyceridaemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. Consider discontinuation of treatment if pancreatitis occurs.

In the HOPE study, the mean percent increase from baseline in serum triglycerides after one year of treatment with PREMARIN 0.625 mg, 0.45 mg and 0.3 mg compared with placebo were 34.3, 30.2, 25.1 and 10.7, respectively. After two years of treatment, the mean percent changes were 47.6, 32.5, 19.0 and 5.5 respectively.

Laboratory monitoring

Estrogen administration should be guided by clinical response instead of by hormone levels, e.g., oestradiol, follicle stimulating hormone (FSH) (see Effects on laboratory tests).

Other

PREMARIN is not an oral contraceptive, nor will it restore fertility. If it is administered, with or without a progestogen, to a woman of child bearing potential she should be advised to use non-hormonal methods of contraception.

Use in the elderly

The estrogen-alone substudy of the WHI reported an increased risk of stroke compared with placebo in postmenopausal women 70 years of age or older. Of the total number of subjects in the estrogen-alone substudy of the Women's Health Initiative study, 46% (n=4,943) were 65 years and over, while 7.1% (n=767) were 75 years and over. There was a higher relative risk (CE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over (see Section 4.4 Special warnings and precautions for use, Cardiovascular risk).

In the estrogen plus progestogen substudy of the WHI, there was a higher relative risk (CE/MPA vs. placebo) of non-fatal stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen plus progestogen combination group compared to the placebo group was 75 vs. 24 per 10,000 women-years and 52 vs. 12 per 10,000 women-years respectively (see Section 4.4 Special warnings and precautions for use, Cardiovascular risk).

The estrogen-alone substudy of the WHIMS, conducted in women aged 65-79, reported an increased risk of developing probable dementia for CE alone compared to placebo (see Section 5.1 Pharmacodynamic properties, Clinical trials and Section 4.4 Special warnings and precautions for use, Dementia).

Seventy nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE group and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both treatment groups and placebo groups was Alzheimer's disease.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings

apply to younger postmenopausal women (see BOXED WARNING and Section 4.4 Special warnings and precautions for use, Dementia).

With respect to efficacy in the approved indications, there have not been sufficient numbers of elderly patients involved in studies utilising PREMARIN to determine whether those over 65 years of age differ from younger subjects in their response to PREMARIN.

Paediatric use

PREMARIN is not indicated for use in paediatrics. Safety and effectiveness in paediatric use has not been established. Estrogen treatment of prepubertal girls induces premature breast development and vaginal cornification and may induce uterine bleeding.

Since large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, hormonal therapy should not be started before epiphyseal closure has occurred in order not to compromise final height.

Effects on laboratory tests

Pathologists should be advised that a patient is receiving estrogen therapy when relevant specimens are submitted.

Certain endocrine and liver function tests may be affected by administration of estrogens.

Accelerated prothrombin time, partial thromboplastin time and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Estrogens increase thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels by column or by radioimmunoassay or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.

Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG) leading to increased circulating corticosteroid and sex steroids respectively. Free or biologically active hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-trypsin, ceruloplasmin).

Impaired glucose tolerance.

The response to metyrapone test may be reduced.

Increased plasma HDL and HDL_2 cholesterol sub-fraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

The results of these tests should not be regarded as reliable until estrogen use has been discontinued for 1-2 months. Abnormal tests results should be repeated.

Gonadotropin levels.

Plasma cortisol levels.

Increased plasma estrogen levels.

4.5 Interactions with other medicines and other forms of interactions

Data from a drug-drug interaction study involving CE and MPA indicate that the pharmacokinetic disposition of both medicines is not altered when the medicines are co-administered. Other clinical drug-drug interaction studies have not been conducted with CE.

In vitro and *in vivo* studies have shown that estrogens are metabolised partially by cytochrome P450 3A4 (CYP3A4). Therefore, CYP3A4 inducers or inhibitors may affect drug metabolism. Inducers of CYP3A4, such as St John's wort (*Hypericum perforatum*) preparations, phenobarbitone, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations of estrogens. This may lead to a decreased effect and/or changes in the uterine bleeding profile. CYP3A4 inhibitors such as cimetidine, erythromycin, clarithromycin, cyclosporin, grapefruit juice, ketoconazole, itraconazole and ritonavir may increase plasma concentrations of estrogens and may result in side effects.

Hot flushes and vaginal bleeding have been reported in patients taking estrogens and St John's wort (*Hypericum perforatum*).

Alteration of the effectiveness of antihypertensive agents, theophyllines, phenothiazines, corticosteroids, tricyclic antidepressants, diazepam and caffeine, by either potentiating/enhancing their pharmacological effect or by decreasing their clearance may occur during estrogen use.

Lamotrigine

Hormonal contraceptives containing estrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. The same interaction has been reported in women taking lamotrigine along with HRT containing estrogens.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category D

PREMARIN should not be used during pregnancy (see Section 4.3 Contraindications).

Estrogens are ineffective in the prevention or treatment of threatened or habitual abortion when given in the first trimester of pregnancy.

If a woman becomes pregnant while using PREMARIN, it should be discontinued immediately.

Use in lactation

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving the drug. Lactating mothers should not use estrogens.

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)

The most serious adverse reactions associated with the use of estrogens are indicated under PRECAUTIONS. The following adverse reactions have been reported and are listed in CIOMS frequency categories as follows:

Very common: ≥10%
Common: ≥1% and <10%
Uncommon: ≥0.1% and <1%
Rare: ≥0.01% and <0.1%
Very rare: <0.01%

Adverse reactions by body system

Immune system disorders

Uncommon: Hypersensitivity.
Rare: Anaphylactic/anaphylactoid reactions, urticaria, angioedema.

Reproductive system and breast disorders

Common: Abnormal uterine bleeding, breast pain, tenderness, enlargement, discharge, leucorrhoea.
Uncommon: Change in menstrual flow, change in cervical ectropion and secretion.
Rare: Galactorrhoea, dysmenorrhoea/pelvic pain, increased size of uterine leiomyomata.
Very rare: Endometrial hyperplasia.

Gastrointestinal disorders

Uncommon: Nausea, bloating, abdominal pain.
Rare: Vomiting, pancreatitis, ischaemic colitis.

Hepatobiliary disorders

Rare: Gallbladder disease.
Very rare: Cholestatic jaundice.

Infections and infestations

Uncommon: Vaginitis including vaginal candidiasis.

Neoplasms benign and malignant (including cysts and polyps)

Rare: Breast cancer, ovarian cancer, fibrocystic breast changes, growth potentiation of benign meningioma.

Very rare: Endometrial cancer, enlargement of hepatic haemangiomas.

Musculoskeletal, connective tissue and bone disorders

Common: Arthralgias, leg cramp.

Psychiatric disorders

Uncommon: Changes in libido, depression, mood disturbances, dementia.
Rare: Irritability.

Skin and subcutaneous tissue disorders

Common: Alopecia.
Uncommon: Chloasma/melasma, hirsutism, rash, pruritis.
Very rare: Erythema multiforme, erythema nodosum.

Cardiac disorders

Rare: Myocardial infarction.

Vascular disorders

Uncommon: Venous thrombosis, pulmonary embolism.
Rare: Superficial thrombophlebitis.

Respiratory, thoracic and mediastinal disorders

Rare: Exacerbation of asthma.

General disorders and administration site conditions

Uncommon: Oedema.

Metabolism and nutrition disorders

Rare: Glucose intolerance.
Very rare: Exacerbation of porphyria, hypocalcaemia (in patients with disease that can predispose to severe hypocalcaemia).

Eye disorders

Uncommon: Steepening of corneal curvature, intolerance to contact lenses.
Very rare: Retinal vascular thrombosis.

Nervous system disorders

Uncommon: Nervousness, dizziness, headache, migraine.
Rare: Exacerbation of epilepsy, stroke.
Very rare: Exacerbation of chorea.

Investigations

Common: Changes in weight (increase or decrease), increased triglycerides.
Very rare: Increase in blood pressure.

Ovarian cancer

Use of estrogen-only or combined estrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed.

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.

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 www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms of overdosage of estrogen-containing products in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment, if necessary, 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

Estrogen production occurs primarily in the ovarian follicles in women from the menarche to the menopause and is important in the development and maintenance of the female urogenital system and secondary sex characteristics.

During the menopause the ovarian-estrogen production decreases and in postmenopausal women, when the ovaries have ceased to function, only a small amount of estrogen is still produced.

This decrease and eventual cessation of estrogen production in perimenopausal and postmenopausal women, respectively, may result in vasomotor symptoms (sweating, hot flushes) and atrophic vaginitis. In addition to relieving or eliminating these disorders, estrogen replacement therapy has also been demonstrated to retard or halt the postmenopausal bone mass loss (osteoporosis).

The pharmacological effects of CE are similar to those of endogenous estrogens.

Clinical trials

Women's Health Initiative studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of oral CE (CE 0.625 mg) alone or in combination with MPA (CE 0.625 mg/MPA 2.5 mg) compared to

placebo. The primary endpoint was the incidence of coronary heart disease (CHD) (non-fatal myocardial infarction (MI), silent MI and CHD death). The primary safety endpoint was the incidence of invasive breast cancer.

A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in CE/MPA), colorectal cancer, hip fracture and death due to other causes. The study did not evaluate the effects of CE alone or CE/MPA on menopausal symptoms.

Estrogen-alone substudy

The estrogen-alone substudy included 10,739 women (average age of 63 years, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other), who were followed up on average for 7.1 years.

The estrogen-alone substudy was stopped early because an increased risk of stroke was observed and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Results of the substudy are presented in Table 1 below. The confidence intervals are unadjusted for multiple looks and multiple comparisons.

Table 1: Relative and absolute risk seen in the estrogen-alone substudy of WHI

Event	**Relative risk (RR) CE vs. Placebo (95% nCI[a])**	**Placebo n = 5,429**	**CE n = 5,310**
		Absolute risk per 10,000 women-years	
CHD events[b]	0.95 (0.79-1.16)	56	53
Non-fatal MI[b]	0.91 (0.73-1.14)	43	40
CHD death[b]	1.01 (0.71-1.43)	16	16
All stroke[c]	1.37 (1.09-1.73)	33	45
Ischaemic[b]	1.55 (1.19-2.01)	25	38
Deep vein thrombosis[b,d]	1.47 (1.06-2.06)	15	23
Pulmonary embolism[b]	1.37 (0.90-2.07)	10	14
Invasive breast cancer[b]	0.80 (0.62-1.04)	34	28
Colorectal cancer[c]	1.08 (0.75-1.55)	16	17
Hip fracture[b]	0.65 (0.45-0.94)	19	12
Vertebral fractures[b,d]	0.64 (0.44-0.93)	18	11
Lower arm/wrist fractures[b,d]	0.58 (0.47-0.72)	59	35
Total fractures[b,d]	0.71 (0.64-0.80)	197	144
Death due to other causes[c,e]	1.08 (0.88-1.32)	50	53
Overall mortality[c,d]	1.04 (0.88-1.22)	78	81
Global Index[c,f]	1.01 (0.91-1.12)	190	192

a: Nominal confidence intervals (nCI) unadjusted for multiple looks and multiple comparisons.
b: Results are based on centrally adjudicated data for an average follow up of 7.1 years.
c: Results are based on an average follow up of 6.8 years.
d: Not included in global index.
e: All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.
f: A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE alone were 12 more strokes while the absolute risk reduction per 10,000 women-years was seven fewer hip fractures. The absolute excess risk of events included in the "global index" was a non-significant two events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality (see BOXED WARNING and Section 4.4 Special warnings and precautions for use).

Final centrally adjudicated results for CHD events and centrally adjudicated results for invasive breast cancer, after an average follow up of 7.1 years, reported no overall difference for primary CHD events (non-fatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE alone compared with placebo (see Table 1).

Centrally adjudicated results for stroke events, after an average follow up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE alone compared to placebo. Estrogen alone increased the risk of ischaemic stroke and this excess was present in all subgroups of women examined (see Table 1).

Estrogen-progestogen substudy

The estrogen plus progestogen substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.8% Black, 5.4% Hispanic, 3.9% Other), was also stopped early. According to the predefined stopping rule, after an average follow up of 5.2 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years (RR 1.15, 95% nCI 1.03-1.28).

For those outcomes included in the WHI "global index", that reached statistical significance after 5.6 years of follow up, the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were six more CHD events, seven more strokes, ten more PEs and eight more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were seven fewer colorectal cancers and five fewer hip fractures (see BOXED WARNING and Section 4.4 Special warnings and precautions for use).

Results of the estrogen plus progestogen substudy are presented in Table 2 below. These results reflect centrally adjudicated data after an average follow up of 5.6 years.

Table 2: Relative and absolute risk seen in the estrogen plus progestogen substudy of WHI at an average of 5.6 years[a]			
Event	**Relative risk (RR) CE/MPA vs. placebo (95% nCI[b])**	**Placebo n = 8,102**	**CE/MPA n = 8,506**
		Absolute risk per 10,000 women-years	
CHD events	1.24 (1.00-1.54)	33	39
Non fatal MI	1.28 (1.00-1.63)	25	31
CHD death	1.10 (0.70-1.75)	8	8
All strokes	1.31 (1.02-1.68)	24	31
Ischaemic stroke	1.44 (1.09-1.90)	18	26
Deep vein thrombosis	1.95 (1.43-2.67)	13	26
Pulmonary embolism	2.13 (1.45-3.11)	8	18
Invasive breast cancer[c]	1.24 (1.01-1.54)	33	41
Invasive colorectal cancer	0.56 (0.38-0.81)	16	9
Endometrial cancer	0.81 (0.48-1.36)	7	6
Cervical cancer	1.44 (0.47-4.42)	1	2
Hip fracture	0.67 (0.47-0.96)	16	11
Vertebral fractures	0.65 (0.46-0.92)	17	11
Lower arm/wrist fractures	0.71 (0.59-0.85)	62	44
Total fractures	0.76 (0.69-0.83)	199	152

a: Results are based on centrally adjudicated data. Mortality data was not part of the adjudicated data, however data at 5.2 years of follow up showed no difference between the groups in terms of all-cause mortality (RR 0.98, 95% nCI 0.82-1.18).
b: Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
C: Includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer.

Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45% were age 65 to 69 years, 36% were 70 to 74 years and 19% were 75 years of age and older) to evaluate the effects of CE 0.625 mg daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow up of 5.2 years, 28 women in the estrogen-alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen-alone group was 1.49 (95% CI, 0.83 to 2.66) compared to placebo. The most common classification of probable dementia in the treatment group and placebo group was Alzheimer's disease. Since the substudy was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women (see BOXED WARNING, Section 4.4 Special warnings and precautions for use, Dementia and Use in the elderly).

The estrogen plus progestogen WHIMS substudy, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47%, age 65 to 69 years; 35%, 70 to 74 years; 18%, 75 years of age and older) to evaluate the effects of CE 0.625 mg/MPA 2.5 mg on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow up of four years, 40 women in the estrogen plus progestogen group (45 per 10,000 woman-years) and 21 in the placebo group (22 per 10,000 women-years) were

diagnosed with probable dementia. The relative risk of probable dementia in the estrogen plus progestogen group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo.

When the data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women (see BOXED WARNING and Section 4.4 Special warnings and precautions for use, Dementia and Use in the elderly).

5.2 Pharmacokinetic properties

Absorption

CE are water soluble and are well absorbed from the gastrointestinal tract after release from the drug formulation. The PREMARIN tablet releases CE slowly over several hours. Table 3 summarises the mean pharmacokinetic parameters for CE following the administration of a single dose of 0.625 mg tablets to healthy postmenopausal women.

Table 3: Pharmacokinetic profile of CE following a single dose of PREMARIN 0.625 mg tablets

PK parameter Arithmetic mean (%CV)	**C_{max} (ng/mL)**	**t_{max} (h)**	**$t_{1/2}$ (h)**	**AUC (ng•h/mL)**
Total estrone	2.7 (43)	6.9 (25)	26.7 (33)	75 (52)
Baseline adjusted total estrone	2.5 (45)	6.9 (25)	14.8 (35)	46 (48)
Total equilin	1.8 (56)	5.6 (45)	11.4 (31)	27 (56)

Metabolism

Metabolism and inactivation occur primarily in the liver.

Excretion

Some estrogens are excreted into the bile; however, they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water soluble estrogen conjugates are strongly acidic and are ionised in body fluids, which favours excretion through the kidneys since tubular reabsorption is minimal.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Studies suggest that combination estrogen and progestogen increases the risk of breast cancer, ovarian cancer and endometrial cancer in women in a time dependant manner (see Section 4.4 Special warnings and precautions for use).

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina and liver.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains lactose monohydrate, hypromellose, magnesium stearate, macrogol 400, sucrose, microcrystalline cellulose, powdered cellulose, hyprolose, calcium phosphate, carnauba wax and Opacode monogramming ink NS-white.

The colouring agent in PREMARIN 0.3 mg tablet is Opadry 152B21511 Green. The colouring agent in PREMARIN 0.625 mg tablet is Opadry 03B16083 Maroon.

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 25°C.

6.5 Nature and contents of container

PREMARIN 0.3 mg and PREMARIN 0.625 mg tablets are available in blister packs PVC/Aclar®/PVC and a hard tempered aluminium foil lid of 28, 56, 84 and 132 tablets.

PREMARIN 0.3 mg tablets are also available in blister packs of 7 tablets.

Not all pack sizes may be marketed.

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

Conjugated estrogens (CE) is a mixture of natural estrogens (of equine origin) composed principally of the sodium salts of water soluble sulfate esters of estrone, equilin and 17α-dihydroequilin together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin, 17β-dihydroequilin, 17β-dihydroequilenin, 17β-estradiol and δ8,9-dihydroestrone.

CAS Number

12126-59-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

30 March 1995.

10. DATE OF REVISION

15 May 2024

Summary Table of Changes

Section changed	Summary of new information
4.4	Editorial changes to provide full explanation of HRT, RR nCI, etc in 1st instance
4.5	Safety update for DDI with lamotrigine
4.8	Update per CIOMS frequency
8	Update for new sponsor website address