NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Premarin® 0.3 mg, 0.625 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Premarin tablet contains 0.3 mg or 0.625 mg conjugated estrogens.

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 17 alpha-dihydroequilin, together with smaller amounts of 17 alpha-estradiol, equilenin, and 17 alpha-dihydroequilenin, 17 beta-dihydroequilin, 17 beta-dihydroequilenin, 17 beta-estradiol and delta 8, 9-dihydroestrone.

Excipient(s) with known effect

Each Premarin 0.3 mg tablet contains 61.7 mg lactose monohydrate and 45 mg sucrose.

Each Premarin 0.625 mg tablet contains 54.1 mg lactose monohydrate and 45 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Premarin 0.3 mg tablet is dark green, oval biconvex sugar-coated and marked with “0.3” in white ink.

Premarin 0.625 mg tablet is maroon, oval biconvex sugar-coated and marked with “0.625” in white ink.

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).
- atrophic vaginitis due to menopause.

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.

For the prevention of postmenopausal osteoporosis

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and future fracture, in whom non-estrogen medications are not considered appropriate.

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

See statements under Section 4.4 Special warnings and precautions for use, General, Malignant neoplasms, Endometrial cancer and Cardiovascular risk and Dementia, particularly when considering Premarin for long-term usage.

4.2 Dose and method of administration

Dose

Continuous daily administration of Premarin is generally recommended.

Patients should be re-evaluated periodically to determine if treatment for symptoms is still necessary. See the statements in Section 4.4 Special warnings and precautions for use, General, Malignant neoplasms, Endometrial cancer and Cardiovascular risk and Dementia, particularly when considering Premarin for long-term usage.

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

For women with an intact uterus, 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.

For prevention of postmenopausal osteoporosis

The minimum effective dose is 0.625 mg daily for most patients.

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.

Method of administration

For oral administration. Tablets should be taken whole; do not divide, crush, chew, or dissolve tablets in mouth.

Premarin tablets can be taken with or without food.

4.3 Contraindications

Premarin is contraindicated in patients with:

- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation, Pregnancy)
- known, suspected or past cancer of the breast
- known or suspected estrogen-dependent neoplasia (e.g., endometrial cancer, endometrial hyperplasia)
- undiagnosed abnormal uterine 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 the active ingredient or any excipients contained in Premarin.

4.4 Special warnings and precautions for use

General

Estrogen therapy and hormone replacement therapy (now referred to as Menopausal Hormone Therapy, MHT) should not be initiated or continued to prevent or treat cardiovascular disease or dementia (see Section 4.4 Special warnings and precautions for use, Cardiovascular risk and Dementia).

The benefits and risks of MHT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. In most circumstances, the risks of long-term MHT outweigh the benefits. 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. In the absence of comparable data, the risks of MHT should be assumed to be similar for all estrogens and estrogen/progestogen combinations.

If prescribing MHT for prevention of osteoporosis, the potential for increased cardiovascular, thrombotic and neoplastic adverse events must be considered.

Physical examination

A complete medical and family history should be obtained prior to initiating or reinstating any estrogen therapy and all prospective and current users of estrogen therapy should be advised of the risks and benefits of estrogens. Pre-treatment and subsequent physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs including histological endometrial assessment and/or papanicolaou smear. Before starting treatment pregnancy should be excluded. Periodic check-ups and careful benefit/risk evaluations should be undertaken in women receiving MHT (see Malignant neoplasms, Endometrial cancer later in this section).

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.

Combined MHT should not be used for the long-term maintenance of general health, including the primary or secondary prevention of cardiovascular disease.

Estrogen or estrogenic compounds must not be used alone as MHT in women who have not had a hysterectomy.

Cardiovascular risk

Estrogen therapy has been reported to increase the risk of stroke and DVT.

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 (VTE)), 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 reported in women receiving estrogen alone compared to women receiving placebo (45 vs. 33 per 10,000 person-years). The increase in risk was observed during year one and persisted. Should a stroke occur or be suspected, estrogens should be discontinued immediately (see Section 5.1 Pharmacodynamic properties, Clinical efficacy and safety).

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 WHI, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or death due to CHD) was reported in women receiving estrogen alone compared to placebo (see Section 5.1 Pharmacodynamic properties, Clinical efficacy and safety).

Venous thromboembolism

In the estrogen alone substudy of WHI, the risk of VTE (DVT and PE), was reported to be increased for women taking CE (30 vs. 22 per 10,000 person-years), although only the increased risk of DVT reached statistical significance (23 vs. 15 per 10,000 person-years). The increase in VTE risk was observed during the first two years. Should a VTE occur or be suspected, estrogens should be discontinued immediately (see Section 5.1 Pharmacodynamic properties, Clinical efficacy and safety, Women's Health Initiative studies).

Recognised risk factors for VTE include, but are not limited to, a personal history or family history of VTE, obesity and systemic lupus erythematosus.

The physician should be aware of the possibility of thrombotic disorders (including thrombophlebitis, retinal thrombosis, cerebral embolism and PE) during MHT and alert to their earliest manifestations. Should any of these occur or be suspected; MHT should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

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.

In the estrogen alone substudy of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg per day) was not associated with an increased risk of invasive breast cancer (RR 0.80, 95% nCI 0.62-1.04).

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. A large meta-analysis of observational studies reported that when estrogen-alone therapy or estrogen-plus-progestin therapy was taken for more than 5 years, the increased risk of breast cancer may persist for 10 years or more after discontinuation of treatment. The reported risk at 10 years or more after discontinuation of treatment was not increased when therapy was taken for less than 5 years. In current users the increased risk of breast cancer in women taking estrogen-alone or combined estrogen-progestin for MHT becomes apparent after about 1-4 years. The risk did not vary by the type of estrogen in estrogen-alone preparations.

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 later in this section).

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. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after ET is discontinued.

Clinical surveillance of all women taking MHT 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 uterine bleeding. Where no pathological cause is found, alteration in the dose or cycling may be indicated (see Section 4.2 Dosage and method of administration).

NOTE: In perimenopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of MHT. An endometrial biopsy may be performed at the discretion of the attending physician.

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. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestogens in estrogen replacement regimens compared to estrogen alone regimens. These include an increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance (see Combined estrogen and progestogen therapy in this section).

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 MHT, 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 MHTs may be associated with a similar or slightly smaller risk (see section 4.8 Undesirable effects).

Dementia

The estrogen alone substudy of the WHIMS, conducted in women aged 65 to 79 years, reported an increased risk of developing probable dementia for CE alone compared to placebo (see Section 4.4 Special warnings and precautions for use, Use in the elderly and Section 5.1 Pharmacodynamic properties, Clinical efficacy and safety, Women's Health Initiative Memory Study).

Therefore, in older women, the use of Premarin for the prevention of osteoporosis should only be considered for those who have failed on, or were intolerant of, non-estrogen medication.

Gallbladder disease

Women receiving Premarin should be monitored for gallbladder disease. A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving MHT has been reported.

Uterine bleeding

Certain patients may develop abnormal uterine bleeding (see Section 4.4 Special warnings and precautions for use, Malignant neoplasms, Endometrial cancer).

Fluid retention

Because estrogens/progestogens may cause some degree of fluid retention, patients with conditions, which 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 with or without vascular involvement, 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. Addition of a progestogen should be considered in women who have undergone hysterectomy but are known to have residual endometriosis, since malignant transformation after estrogen only therapy has been reported.

Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure during estrogen therapy 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 with estrogen use.

Impaired liver function and history of cholestatic jaundice

Estrogens may be poorly metabolised in patients with impaired liver function (see Section 4.3 Contraindications). If jaundice develops in any patient receiving estrogen, the medication should be discontinued.

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, Premarin should be discontinued.

Angioedema

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

Hypercalcaemia

Premarin should be used with caution in patients with metabolic bone disease that is associated with hypercalcaemia or in patients with renal insufficiency.

Hypocalcaemia

Estrogens should be used with caution in patients with severe hypocalcaemia, and in diseases that can predispose to severe hypocalcaemia.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients dependent on thyroid replacement therapy, who are receiving estrogens, may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range (see Effects on laboratory tests later in this section).

Visual abnormalities

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

Hypertriglyceridaemia

Estrogen may increase plasma triglyceride levels, which is a risk factor for pancreatitis and other complications. Caution should be exercised in patients with pre-existing

hypertriglyceridaemia since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this population. Women with pre-existing hypertriglyceridaemia should be followed closely during MHT.

Laboratory monitoring

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

Other

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

Effects on laboratory tests

Pathologists should be made aware that a patient is receiving MHT when relevant specimens are submitted.

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

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 then be repeated.

Gonadotropin levels.

Plasma cortisol levels.

Increased plasma estrogen levels.

Use in the elderly

The WHI estrogen alone substudy reported an increased risk of stroke compared with placebo in postmenopausal women 65 years of age or older (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. It is unknown whether these findings apply to younger postmenopausal women (see Section 4.4 Special warnings and precautions for use, Dementia and Section 5.1 Clinical efficacy and safety, Women's Health Initiative Memory Study).

Paediatric population

Premarin is not indicated for use in paediatrics. Safety and effectiveness in paediatric patients have not been established. Estrogen treatment of prepubertal girls also 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, MHT should not be started before epiphyseal closure has occurred in order not to compromise final growth.

4.5 Interaction with other medicines and other forms of interaction

Data from a drug-drug interaction study involving Premarin and medroxyprogesterone acetate 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 Premarin.

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 receiving MHT 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 lamotrigine effectiveness including seizure control. The same interaction has been reported in women taking lamotrigine along with MHT containing estrogens.

4.6 Fertility, pregnancy and lactation

Pregnancy

Australian pregnancy Category D

Premarin should not be used during pregnancy.

Lactation

Lactating mothers should not use Premarin. 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.

4.7 Effects on ability to drive and use machinery

No studies on the effect of ability to drive or use machinery have been performed.

4.8 Undesirable effects

The most serious adverse reactions associated with the use of Premarin are indicated under Section 4.4 Special warnings and precautions for use. The following adverse reactions have been reported and are listed below in CIOMS frequency categories:

Adverse reactions as per CIOMS frequency categories by body system:

Very common: ≥10%
Common: ≥1% and <10%
Uncommon: ≥0.1% and <1%
Rare: ≥0.01% and <0.1%
Very rare: <0.01%
Unknown: cannot be estimated from the available data.

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.

Immune system disorders

Uncommon: Hypersensitivity.

Rare: Urticaria, angioedema, anaphylactic/anaphylactoid reactions.

Metabolism and nutrition disorders

Rare: Glucose intolerance.

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

Psychiatric disorders

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

Rare: Irritability.

Nervous System disorders

Uncommon: Dizziness, headache, migraine, nervousness.

Rare: Cerebrovascular accident/stroke, exacerbation of epilepsy.

Very rare: Exacerbation of chorea.

Eye Disorders

Uncommon: Intolerance to contact lenses.

Very rare: Retinal vascular thrombosis.

Cardiac disorders

Rare: Myocardial infarction.

Vascular disorders

Uncommon: Venous thrombosis, pulmonary embolism.

Rare: Superficial thrombophlebitis.

Respiratory, thoracic and mediastinal disorders

Rare: Exacerbation of asthma.

Gastrointestinal disorders

Uncommon: Nausea, bloating, abdominal pain.

Rare: Vomiting, pancreatitis, ischaemic colitis.

Hepatobiliary disorders

Uncommon: Gallbladder disease.

Very rare: Cholestatic jaundice.

Skin and subcutaneous tissue disorders

Common: Alopecia.

Uncommon: Chloasma/melasma, hirsutism, pruritus, rash.

Very rare: Erythema multiforme, erythema nodosum.

Musculoskeletal, connective tissue and bone disorders

Common: Arthralgias, leg cramp.

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: Dysmenorrhoea/pelvic pain, galactorrhoea, increased size of uterine leiomyomata.

Very rare: Endometrial hyperplasia

Unknown: Gynaecomastia in males.

General disorders and administration site conditions

Uncommon: Oedema.

Investigations

Common: Changes in weight (increase or decrease), increased triglycerides.

Very rare: Increase in blood pressure.

Ovarian cancer

Use of estrogen-only and or combined estrogen-progestogen MHT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4 Special warnings and precautions for use, Malignant neoplasms, Ovarian cancer).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using MHT compared to women who have never used MHT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of MHT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking MHT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professionals are asked to report any suspected adverse reactions (https://pophealth.my.site.com/carmreportnz/s/).

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 efficacy and safety

Women's Health Initiative studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two sub-studies to assess the risks and benefits of CE (0.625 mg daily) alone or in combination with medroxyprogesterone acetate (MPA) (0.625 mg/2.5 mg daily) compared to placebo. The primary endpoint was incidence of coronary heart disease (CHD), i.e., non-fatal myocardial infarction (MI), silent MI and coronary death. The primary safety endpoint was incidence of invasive breast cancer. The study did not evaluate the effects of MHT on menopausal symptoms.

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.

No overall effect on CHD events (defined as non-fatal MI, silent MI, or death, due to CHD) was reported in women receiving estrogen alone compared to placebo. Results of the estrogen alone substudy, which 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) after an average follow-up of 6.8 years are presented in the table below.

In the estrogen alone substudy of WHI, there was no significant overall effect on the relative risk (RR) of CHD (RR 0.95, 95% nominal confidence interval (nCI) 0.78- 1.16); a slightly elevated RR of CHD was reported in the early follow-up period and diminished over time. There was no significant effect on the RR of invasive breast cancer (RR 0.80, 95% nCI 0.62-1.04) or colorectal cancer (RR 1.08, 95% nCI 0.75-1.55) reported. Estrogen use was associated with a statistically significant increased risk of stroke (RR 1.33, 95% nCI 1.05-1.68) and deep vein thrombosis (DVT) (RR 1.47, 95% nCI 1.06-2.06). The RR of pulmonary embolism (PE) (RR 1.37, 95% nCI 0.90-2.07) was not significantly increased. A statistically significant reduced risk of hip, vertebral and total fractures was reported with estrogen use (RR 0.65, 95% nCI 0.45-0.94), (RR 0.64, 95% nCI 0.44-0.93), and (RR 0.71, 95% nCI 0.64-0.80), respectively. The estrogen alone substudy did not report a statistically significant effect on death due to other causes (RR 1.08, 95% nCI 0.88-1.32) or an effect on overall mortality risk (RR 1.04, 95% nCI 0.88-1.22).

These confidence intervals are unadjusted for multiple looks and multiple comparisons.

Relative and Absolute Risk seen in the Estrogens Alone Substudy of WHI			
Event	**Relative Risk ET(estrogen therapy) vs. Placebo (95% nCI[a])**	**Placebo (n = 5,429)**	**ET (n = 5,310)**
		Absolute Risk per 10,000 person-years	
CHD events[b]	0.95 (0.78-1.16)	57	54
Non-fatal MI[b]	0.91 (0.73-1.14)	43	40
CHD death[b]	1.01 (0.71-1.43)	16	16
Stroke[b]	1.33 (1.05-1.68)	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[b,d]	1.04 (0.88-1.22)	75	79
Global Index[f]	1.02 (0.92-1.13)	201	206

[a] Nominal confidence intervals 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.

Final adjudicated results for CHD events from the estrogen alone substudy, 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) in women receiving CE compared with placebo.

Observational Studies of Breast Cancer Risk

A large meta-analysis of observational studies generated evidence for the type and timing of MHT on breast cancer risk. After ceasing MHT, some excess risk persisted for more than 10 years; its magnitude depended on the duration of previous use.

It was reported that, when estrogen alone therapy or estrogen plus progestin therapy was taken for more than 5 years, the increased risk may persist for 10 years or more after discontinuation of treatment:

MHT type	**Time passed since discontinuation of MHT**	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen-alone	≥10 years	5-9 years	1.14 (1.04-1.25)
	≥10 years	≥10 years	1.29 (1.16-1.42)
Estrogen+progestin	≥10 years	5-9 years	1.19 (1.10-1.28)
	≥10 years	≥10 years	1.28 (1.15-1.43)

The reported risk at 10 years or more after discontinuation of treatment was not increased when therapy was taken for less than 5 years:

MHT type	**Time passed since discontinuation of MHT**	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen-alone	≥10 years	<1 year	0.99 (0.87-1.12)
	≥10 years	1-4 years	1.04 (0.95-1.13)
Estrogen+progestin	≥10 years	<1 year	1.06 (0.95-1.19)
	≥10 years	1-4 years	1.09 (1.00-1.18)

In current users, the increased risk of breast cancer in women taking estrogen-alone or combined estrogen-progestin MHT becomes apparent after about 1-4 years:

MHT type	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen-alone	<1 year	1.08 (0.86-1.35)
	1-4 years	1.17 (1.10-1.26)
Estrogen+progestin	<1 year	1.20 (1.01-1.43)
	1-4 years	1.60 (1.52-1.69)

The risk did not vary by the type of estrogen in estrogen-alone preparations:

Estrogen-alone MHT by constituent	Duration of MHT therapy	Risk ratio (95% CI)
Equine estrogen	5-14 years	1.32 (1.25-1.39)
Estradiol	5-14 years	1.38 (1.30-1.46)

In the estrogen alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 2,947 predominantly healthy hysterectomised women, aged 65-79 years, was randomised to CE (0.625 mg daily) or placebo. 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. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and placebo group was AD. Since this study was conducted in women aged 65-79 years, it is unknown whether these findings apply to younger postmenopausal women (see Section 4.4 Special warnings and precautions for use, Dementia).

5.2 Pharmacokinetic properties

Absorption

CE are soluble in water and are well absorbed from the gastrointestinal tract. The Premarin tablet releases CE slowly over several hours. Table 1 summarises the mean pharmacokinetic parameters for CE following the administration of a single dose of 0.625 mg tablets to healthy postmenopausal women.

Table 1: Pharmacokinetic profile of Premarin following a single dose of 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)

Biotransformation

Metabolism and inactivation occur primarily in the liver.

Elimination

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

Carcinogenicity

Studies suggest that combination MHT 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

- Lactose monohydrate
- Hypromellose
- Magnesium stearate
- Macrogol 400
- Sucrose
- Microcrystalline cellulose
- Hyprolose
- Carnauba wax
- Opacode WB NS-78-1-18011 white ink.

Premarin 0.3 mg tablets contain the colouring agent opadry green 15B21511.

Premarin 0.625 mg tablets contain the colouring agent opadry maroon 03B16083.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Premarin 0.3 mg and 0.625 mg tablets are supplied in PVC/Aclar/PVC/Al blister packs of 28 tablets.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand.
www.pfizermedicalinformation.co.nz

Toll Free Number: 0800 736 363.

9. DATE OF FIRST APPROVAL

5 February 1991.

10. DATE OF REVISION OF THE TEXT

04 December 2024

Summary table of changes

Section changed	Summary of new information
Throughout	Minor editorial changes, including replacement of term Hormone Therapy and Hormone Replacement Therapy (HRT) to Menopausal Hormone Therapy (MHT)
4.4 & 5.1	Addition of further information related to the known risk of breast cancer
4.4	Addition of risk of elevated triglycerides and pancreatitis

® Registered trademark.