

PREMARIN[®] TABLETS

(Conjugated oestrogens USP tablets)

NAME OF MEDICINE

PREMARIN Tablets

DESCRIPTION

PREMARIN (conjugated oestrogens), is a mixture of natural oestrogens (of equine origin) composed principally of the sodium salts of water-soluble sulfate esters of oestrone, equilin, and 17 alpha-dihydroequilin, together with smaller amounts of 17 alpha-oestradiol, equilenin, and 17 alpha-dihydroequilenin, 17 beta-dihydroequilin, 17 beta-dihydroequilenin, 17 beta-oestradiol and delta 8, 9-dihydroestrone.

Each tablet contains lactose, methylcellulose, magnesium stearate, shellac solution, macrogol 20000, glyceryl mono-oleate, calcium sulfate, sucrose, microcrystalline cellulose, titanium dioxide, carnauba wax, stearic acid and Ink White Opacode S-8-28905.

The colouring agent in PREMARIN 0.3mg tablets is Opalux Green, which contains sodium benzoate, iron oxide yellow (CI 77492), indigo carmine (CI 73015), methyl hydroxybenzoate and propyl hydroxybenzoate.

The colouring agent in PREMARIN 0.625 mg tablets is Opalux Maroon, which contains sodium benzoate, erythrosine (CI 45430), sunset yellow FCF (CI 15985), titanium dioxide and indigo carmine (CI 73015).

PHARMACOLOGY

Pharmacodynamics

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

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

The pharmacological effects of conjugated oestrogens are similar to those of endogenous oestrogens.

Pharmacokinetics

Conjugated oestrogens are soluble in water and are well absorbed from the gastrointestinal tract. Metabolism and inactivation occur primarily in the liver. Some oestrogens are excreted into the bile; however, they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water-soluble oestrogen conjugates are strongly acidic and are ionised in body fluids, which favours excretion through the kidneys since tubular reabsorption is minimal.

CLINICAL TRIALS

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 conjugated oestrogen [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 hormone replacement therapy on menopausal symptoms.

The oestrogen 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 oestrogen alone in predetermined primary endpoints.

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 oestrogen alone compared to placebo. Results of the oestrogen 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 oestrogen 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. Oestrogen 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 oestrogen 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 oestrogen 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 OESTROGEN ALONE SUBSTUDY OF WHI			
Event	Relative Risk ET 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 oestrogen-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 conjugated oestrogens compared with placebo.

Women’s Health Initiative Memory Study

In the oestrogen-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 conjugated oestrogens (0.625 mg daily) or placebo. The relative risk of probable dementia for conjugated oestrogens alone vs. placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for oestrogen-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 PRECAUTIONS - *Dementia*).

INDICATIONS

Oestrogens 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:

- 1) As replacement therapy for oestrogen deficiency states associated with climacteric manifested by:
 - a) Moderate to severe vasomotor symptoms associated with the oestrogen deficiency in natural and surgical menopause (sweating, hot flushes).
 - b) 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 oestrogens are effective for anxiety or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.

- 2) 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-oestrogen medications are not considered appropriate.

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

See the statements in bold under PRECAUTIONS, particularly when considering PREMARIN for long-term usage.

CONTRAINDICATIONS

Known or suspected pregnancy (See *Use in Pregnancy*)

Known, suspected or past cancer of the breast

Known or suspected oestrogen-dependent neoplasia (e.g. endometrial cancer, endometrial hyperplasia)

Undiagnosed abnormal uterine bleeding

Active or past 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 any ingredients contained in PREMARIN.

PRECAUTIONS

Oestrogen therapy and hormone therapy should not be initiated or continued to prevent or treat cardiovascular disease or dementia (See PRECAUTIONS - *Cardiovascular Risk* and PRECAUTIONS - *Dementia*).

The benefits and risks of hormone therapy must always be carefully weighed, including consideration of the emergence of risks as therapy continues. In most circumstances, the risks of long-term hormone therapy outweigh the benefits. Oestrogens 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 hormone therapy should be assumed to be similar for all oestrogens and oestrogen/progestogen combinations.

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

Combined Oestrogen and Progestogen Therapy

There are additional and/or increased risks that may be associated with the use of combination oestrogen-progestogen therapy compared with using oestrogen-alone regimens. These include an increased risk of myocardial infarction, pulmonary embolism, invasive breast cancer and ovarian cancer.

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

Oestrogen or oestrogenic compounds must not be used alone as hormone therapy in women who have not had a hysterectomy.

Cardiovascular Risk

Oestrogen therapy has been reported to increase the risk of stroke and deep vein thrombosis (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 VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the oestrogen-alone substudy of the WHI, a statistically significant increased risk of stroke was reported in women receiving oestrogen 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, oestrogens should be discontinued immediately (See 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 oestrogen-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 oestrogen alone compared to placebo (See CLINICAL TRIALS).

Venous Thromboembolism

In the oestrogen-alone substudy of WHI (See CLINICAL TRIALS - *Women's Health Initiative*) the risk of VTE (DVT and pulmonary embolism), was reported to be increased for women taking conjugated oestrogens (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, oestrogens should be discontinued immediately (See CLINICAL TRIALS).

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 pulmonary embolism) during hormone replacement therapy and alert to their earliest manifestations. Should any of these occur or be suspected; hormone therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

If feasible, oestrogens 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 oestrogens by postmenopausal women have reported inconsistent results on the risk of breast cancer.

In the oestrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, conjugated oestrogens (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 oestrogen-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 of stopping).

The use of oestrogen alone and oestrogen 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 oestrogens 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 oestrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on oestrogen dose. Most studies show no significant increased risk associated with use of oestrogens 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 hormone therapy 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 DOSAGE AND ADMINISTRATION).

NOTE: In perimenopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of hormone replacement therapy. 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 oestrogen administration or daily with oestrogen in a continuous regimen, have reported a lower incidence of endometrial hyperplasia than would be induced by oestrogen 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 oestrogen replacement regimens compared to oestrogen alone regimens. These include (a) an increased risk of breast cancer; (b) adverse effects on lipoprotein metabolism (e.g. lowering HDL, raising LDL); and (c) impairment of glucose tolerance (See *Combined Oestrogen and Progestogen Therapy*).

Ovarian Cancer

In some epidemiological studies, the use of oestrogen-only products has been associated with an increased risk of ovarian cancer over multiple years of use. Other epidemiological studies have not found these associations.

Dementia

A substudy of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of conducted in women aged 65 to 79 years reported an increased risk of developing probable dementia when compared with placebo (See CLINICAL TRIALS and *Use in the Elderly*).

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-oestrogen medication.

Physical Examination

A complete medical and family history should be obtained prior to initiating or reinstating any oestrogen therapy and all prospective and current users of oestrogen therapy should be advised of the risks and benefits of oestrogens (See PRECAUTIONS). Pretreatment 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 hormone therapy (See *Endometrial Cancer*).

Gallbladder Disease

Women receiving PREMARIN should be monitored for gall-bladder disease. A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving hormone therapy has been reported.

Uterine Bleeding

Certain patients may develop abnormal uterine bleeding (See *Endometrial Cancer*).

Fluid Retention

Because oestrogens/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 oestrogens are prescribed.

Exacerbation of Other Conditions

Oestrogen 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 hemangiomas and should be used with caution in women with these conditions.

Endometriosis may be exacerbated with administration of oestrogen 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 oestrogen only therapy has been reported.

Elevated Blood Pressure

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

Impaired Liver Function and Past History of Cholestatic Jaundice

Oestrogens may be poorly metabolised in patients with impaired liver function (See CONTRAINDICATIONS). If jaundice develops in any patient receiving oestrogen, the medication should be discontinued.

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

Angioedema

Exogenous oestrogens 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

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

Hypothyroidism

Oestrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients dependent on thyroid replacement therapy, who are receiving oestrogens, 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 *Laboratory Test Interactions*).

Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving oestrogens. 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

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 oestrogen therapy in this population. Women with pre-existing hypertriglyceridaemia should be followed closely during hormone therapy.

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.

Use in Paediatrics

See INDICATIONS. Safety and effectiveness in paediatric patients have not been established. Oestrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce uterine bleeding.

Since large and repeated doses of oestrogen 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 growth.

Use in the Elderly

The oestrogen-alone substudy of the Women's Health Initiative (WHI) reported an increased risk of stroke compared with placebo in postmenopausal women 65 years of age or older (See *Cardiovascular Risk*).

A substudy of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI conducted in women aged 65-79, reported an increased risk of developing probable dementia when compared with placebo. It is unknown whether these findings apply to younger postmenopausal women. (See *Dementia* and CLINICAL TRIALS).

Use in Pregnancy

Category D

PREMARIN should not be used during pregnancy.

Use during Lactation

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

Carcinogenic Potential

Studies suggest that combination hormone therapy increases the risk of breast cancer, ovarian cancer and endometrial cancer in women in a time dependant manner (See PRECAUTIONS).

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

Interactions with Other Medicines

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 oestrogens 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 oestrogens. 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 oestrogens and may result in side effects.

Hot flushes and vaginal bleeding have been reported in patients receiving hormone therapy and St John's Wort (*Hypericum perforatum*).

Laboratory Test Interactions

Pathologists should be made aware that a patient is receiving hormone therapy 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.

Oestrogens increase thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T₄ levels by column or by radioimmunoassay or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered.

Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG) leading to increased circulating corticosteroid and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. 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 HDL₂ cholesterol sub-fraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

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

Gonadotropin levels.

Plasma cortisol levels.

Increased plasma oestrogen levels.

ADVERSE EFFECTS

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

Adverse reactions as per CIOMS frequency categories:

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: Urticaria, angioedema, anaphylactic/anaphylactoid reactions

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

Gastrointestinal Disorders

Uncommon: Nausea, bloating, abdominal pain

Rare: Vomiting, pancreatitis, ischaemic colitis

Hepato-biliary Disorders

Uncommon: 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 hemangiomas

Musculoskeletal, Connective Tissue and Bone Disorders

Common: Arthralgias, leg cramp

Psychiatric Disorders

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

Rare: Irritability

Skin and Subcutaneous Tissue Disorders

Common: Alopecia

Uncommon: Chloasma/melasma, hirsutism, pruritis, rash,

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: Intolerance to contact lenses

Very Rare: Retinal vascular thrombosis

Nervous System Disorders

Uncommon: Dizziness, headache, migraine, nervousness

Rare: Cerebrovascular accident/stroke, exacerbation of epilepsy

Very Rare: Exacerbation of chorea

Investigations

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

Very Rare: Increase in blood pressure

DOSAGE AND ADMINISTRATION

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 bold under PRECAUTIONS, particularly when considering PREMARIN for long-term usage.

For women with an intact uterus, it is recommended that a progestogen is administered (See PRECAUTIONS – *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 PRECAUTIONS – *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 oestrogen course.

Usual Dosage Ranges:

1) 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.

2) For prevention of postmenopausal osteoporosis

The minimum effective dose is 0.625mg 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.

3) 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 oestrogen 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 oestrogen-progestogen cyclic regimen with PREMARIN, 2.5 to 7.5 mg daily in divided doses. During the last five days of oestrogen 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.

OVERDOSAGE

Symptoms of overdosage of oestrogen-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.

PRESENTATION AND STORAGE CONDITIONS

Tablets:

0.3 mg (dark green, marked 0.3): 1 x 28's

0.625 mg (maroon, marked 0.625): 1 x 28's.

Store below 30°C

MEDICINES CLASSIFICATION

Prescription Only Medicine

NAME AND ADDRESS

Pfizer New Zealand Ltd

PO Box 3998

Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363

® Registered Trade Mark

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* Please note changes to Data Sheet.