℞

CONJUGATED ESTROGENS

PREMARIN®

300 mcg and 625 mcg Tablet

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens 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.

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in post-menopausal women during 5 years of treatment with conjugated estrogens (625 mcg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see **section 5.1 Pharmacodynamic Properties** – *Clinical Efficacy*). Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risk should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1.0 PHARMACOLOGIC CATEGORY

Sex Hormone and Modulator of the Genital System (Estrogen)

2.0 DESCRIPTION

Conjugated Estrogens (Premarin) for oral administration is a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains the sodium salts of water-soluble sulfate esters of estrone, equilin, and 17 alpha-dihydroequilin, together with smaller amounts of 17 alpha-estradiol, equilenin, 17 alpha-dihydroequilenin, 17 beta-dihydroequilin, 17 beta-dihydroequilenin, 17 beta-estradiol, and delta 8, 9-dehydroestrone.

3.0 FORMULATION/ COMPOSITION

Conjugated Estrogens (Premarin) 300 mcg tablets: Each tablet contains 300 mcg of Conjugated Estrogens

Conjugated Estrogens (Premarin) 625 mcg tablets: Each tablet contains 625 mcg of Conjugated Estrogens

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Treatment of moderate to severe vasomotor symptoms due to menopause.
2. Treatment of vulvar and vaginal atrophy due to menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Prevention of post-menopausal osteoporosis in women at risk of future fractures.
4. Treatment of female hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

4.2 Dosage and Method of Administration

The benefits and risks of Estrogen Therapy (ET) must always be carefully weighed, including consideration of the emergence of risks as therapy continues (see **section 4.4 Special Warnings and Precautions for Use**). Estrogens with or without progestins 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 ET should be assumed to be similar for all estrogens and estrogen/progestin combinations.

Usual Dosage Range
Vasomotor Symptoms, Atrophic Vaginitis, and Atrophic Urethritis Associated with Estrogen Deficiency: 300 mcg - 1.25 mg daily. Estrogen deficient women who are being treated for these conditions should be evaluated at regular intervals (3 - 6 months).

Osteoporosis: 625 mcg daily. This dose is required for bone mass conservation.

Female Hypoestrogenism: 300 mcg - 1.25 mg daily. Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium. Doses of 150 mcg have been used in girls and are associated with the onset of development of secondary sex characteristics. Dose should be individualized to achieve optimum patient response.

Patients should be reevaluated periodically to determine if treatment for symptoms is still necessary.

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

Treatment of moderate to severe vasomotor symptoms and/or vulvar and vaginal atrophy associated with menopause.

If an estrogen is prescribed for a post-menopausal woman with a uterus, the addition of a progestin may be appropriate (see **section 4.4 Special Warnings and Precautions for Use -** *Malignant Neoplasms*). In some cases, hysterectomized women with a history of endometriosis may need a progestin (see **section 4.4 Special Warnings and Precautions for Use -***Exacerbation of other conditions*).

In a 52-week trial using conjugated estrogens vaginal cream alone (in the absence of any progestin), 0.5 g twice weekly or 0.5 g 3 weeks on and 1 week off, there was no evidence of endometrial hyperplasia or endometrial carcinoma.

Consider topical vaginal products when treating solely for vulvar and vaginal atrophy.

<u>Prevention of post-menopausal osteoporosis</u>

- When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered

Treatment of female hypogonadism

- Administer cyclically (e.g., three weeks on and one week off).

Treatment of female castration or primary ovarian failure

- Administer cyclically (e.g., three weeks on and one week off).

Use in children

Safety and effectiveness in pediatric patients have 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 growth.

Use in elderly patients

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Conjugated Estrogens to determine whether those over 65 years of age differ from younger subjects in their response to Conjugated Estrogens.

The Women's Health Initiative Study (WHI)

In the WHI estrogen-alone substudy (daily CE [0.625 mg] versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age (see **section 5.1 Pharmacodynamic properties**, *WHI Studies*).

The Women's Health Initiative Memory Study (WHIMS)

In the WHIMS of postmenopausal women 65 to 79 years of age, there was increased risk of developing probable dementia in women receiving estrogen alone when compared to placebo. It is unknown whether this finding applies to younger postmenopausal women. (see **section 4.4 Special Warnings and Precautions for Use**, *Dementia* and **section 5.1 Pharmacodynamic properties**, *WHIM Study*)

4.3 Contraindications

1. Known or suspected pregnancy (see **section 4.6 Fertility, Pregnancy and Lactation**).
2. Undiagnosed abnormal uterine bleeding.
3. Known, suspected or history of breast cancer.
4. Known or suspected estrogen-dependent neoplasia (e.g. endometrial cancer, endometrial hyperplasia).
5. Active or history of arterial thromboembolic disease (e.g. stroke, myocardial infarction) or venous thromboembolism such as deep venous thrombosis, pulmonary embolism).
6. Active or chronic liver dysfunction or disease.
7. Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency).
8. Known or suspected hypersensitivity to any of the components of Conjugated Estrogens (Premarin) Tablets.

4.4 Special Warnings and Precautions for Use

General

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

Cardiovascular Risk
ET has been reported to increase the risk of stroke and deep venous thrombosis (DVT).

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

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

Stroke
In the Women's Health Initiative (WHI) estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) compared to women receiving placebo (45 vs. 33 per 10,000 women-years). The increase in risk was observed during year one and persisted.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) versus those receiving placebo (18 versus 21 per 10,000 women-years).

Should a stroke occur or be suspected, Conjugated estrogens should be discontinued immediately (see **section 5.1 Pharmacodynamic Properties –** *Clinical Efficacy*).

Venous thromboembolism
In the estrogen-alone substudy of WHI, the increased risk of deep venous thrombosis (DVT) was reported to be statistically significant (23 vs. 15 per 10,000 person-years). The risk of pulmonary embolism (PE) was reported to be increased, although it did not reach statistical significance. The increase in venous thromboembolism (VTE,DVT and PE) risk was demonstrated during the first two years (30 vs. 22 per 10,000 person-years).

Should a VTE occur or be suspected, Conjugated estrogens should be discontinued immediately (see **section 5.1 Pharmacodynamic Properties –** *Clinical Efficacy*).

If visual abnormalities develop, discontinue Conjugated estrogens pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. Retinal vascular thrombosis has been reported in patients receiving estrogens with or without progestins.

If feasible, Conjugated estrogens should be discontinued at least four to six weeks before surgery of the type associated with an increased risk of thromboembolism,

or during periods of prolonged immobilization.

Malignant Neoplasms

Endometrial cancer
The use of unopposed estrogens in women with an intact-uterus has been associated with an increased risk of endometrial cancer (see **section 4.4 Special Warnings and Precautions for Use -** *Exacerbation of other Conditions* and **section 5.1 Pharmacodynamic Properties –** *Clinical Efficacy*).

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 5 to 10 years or more, and this risk has been shown to persist for at least 8-15 years after ET is discontinued. Adding a progestin to post-menopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer (see **section 4.4 Special Warnings and Precautions for Use -** *General*).

Clinical surveillance of all women taking estrogen or estrogen-plus-progestin combinations is important. Adequate diagnostic measures should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal uterine bleeding.

Breast cancer
Studies involving the use of estrogens by post-menopausal women have reported inconsistent results on the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) (see **section 5.1 Pharmacodynamic Properties –** *Clinical Efficacy*). In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CE (625 mcg daily) was not associated with an increased risk of invasive breast cancer.

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 use of estrogen has been reported to result in an increase in abnormal mammograms requiring further evaluation.

Ovarian cancer
In some epidemiologic studies, the use of estrogen-only products has been associated with an increased risk of ovarian cancer over multiple years of use.

Other epidemiologic studies have not found these associations.

Dementia
The estrogen-alone arm of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI that enrolled post-menopausal women between the ages of 65-79 reported a relative risk (HR) of probable dementia for conjugated estrogens alone versus placebo of 1.49 [HR 1.49 (95% CI 0.83-2.66)] (see **section 5.1 Pharmacodynamic Properties**).

It is unknown whether these findings apply to younger post-menopausal women.

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

Immune

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

Fluid Retention
Because estrogens 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.

Hypertriglyceridemia
In the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, the mean percent increases from baseline in serum triglycerides after one year of treatment with CE 0.625 mg, 0.45 mg, 300 mcg and placebo were 34.2, 30.2, 25.0, and 10.8, respectively.

Caution should be exercised in patients with pre-existing hypertriglyceridemia since rare cases of large increases of plasma trigylcerides leading to pancreatitis have been reported with estrogen therapy in this population.

Impaired Liver Function and 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. Estrogens may be poorly metabolized in patients with impaired liver function.

Elevated Blood Pressure
In a small number of case reports, substantial increases in blood pressure during ET have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial a generalized effect of ET on blood

pressure was not seen.

Exacerbation of Other Conditions
Estrogen replacement therapy may cause an exacerbation of asthma, epilepsy, migraine with or without aura, 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 ET. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

Hypocalcemia
Estrogens should be used with caution in individuals with disease that can predispose to severe hypocalcemia.

Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients dependent on thyroid hormone 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 **section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Laboratory Monitoring
Estrogen administration should be guided by clinical response rather than by hormone levels (e.g. estradiol, FSH).

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Data from a drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs is not altered when the drugs are co-administered. Other clinical drug-drug interaction studies have not been conducted with conjugated estrogens.

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit

juice, may increase plasma concentrations of estrogens and may result in side effects.

Interference with Laboratory and Other Diagnostic Tests

Laboratory Test Interactions
Increased platelet count decreased levels of antithrombin III, and 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.

Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

The response to metyrapone may be reduced.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Conjugated Estrogens should not be used during pregnancy (see **section 4.3 Contraindications**).

If pregnancy occurs during medication with conjugated estrogens treatment should be withdrawn immediately.

Lactation
Conjugated Estrogens should not be used during 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. Caution should be exercised when estrogens are administered to a nursing woman.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

Adverse reactions are listed in the Table in 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%

System Organ Class Adverse Reaction

Reproductive system and breast disorders

Common:	Abnormal uterine bleeding; breast pain, tenderness, enlargement, discharge; leukorrhea
Uncommon:	Change in menstrual flow; change in cervical ectropion and secretion
Rare:	Dysmenorrhea/pelvic pain; galactorrhea; increased size of uterine leiomyomata
Very rare:	Endometrial hyperplasia
Unknown:	Gynecomastia in males

Gastrointestinal disorders

Uncommon:	Nausea; bloating; abdominal pain
Rare:	Vomiting; pancreatitis; ischemic colitis

Nervous system disorders

Uncommon:	Dizziness; headache; migraine; nervousness
Rare:	Cerebrovascular accident/stroke; exacerbation of epilepsy
Very rare:	Exacerbation of chorea

Musculoskeletal, connective tissue and bone disorders

Common:	Arthralgias; leg cramps

Psychiatric disorders

Uncommon:	Changes in libido; mood disturbances; depression; dementia
Rare:	Irritability

Vascular disorders

Uncommon:	Venous thrombosis; pulmonary embolism
Rare:	Superficial thrombophlebitis

General disorders and administration site conditions

Uncommon:	Edema

Skin and subcutaneous tissue disorders

Common:	Alopecia
Uncommon:	Chloasma/melasma; hirsutism; pruritus; rash
Very rare:	Erythema multiforme; erythema nodosum

Hepato-biliary disorder

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

Immune system disorders

Uncommon:	Hypersensitivity
Rare:	Urticaria, angioedema; anaphylactic/anaphylactoid reactions

Metabolism and nutrition disorders

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

Eye disorders

Uncommon:	Intolerance to contact lenses
Very rare:	Retinal vascular thrombosis

Cardiac disorders

Rare:	Myocardial infarction

Respiratory, thoracic and mediastinal disorders

Rare:	Exacerbation of asthma

Investigations

Common:	Changes in weight (increase or decrease); increased triglycerides
Very rare:	Increases in blood pressure

4.9 Overdose and Treatment

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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, which is secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in post-menopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in post-menopausal women.

Pharmacodynamics

Currently, there are no pharmacodynamic data known for Conjugated Estrogens (CE) alone.

Effects on vasomotor symptoms

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2,805 post-menopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups, receiving either placebo or conjugated estrogens, with or without medroxyprogesterone acetate. Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least seven moderate-to-severe hot flushes daily, or at least 50 moderate-to-severe hot flushes during the

week before randomization. With CE (300 mcg, 450 mcg, and 625 mcg tablets), the decrease of both the frequency and severity of moderate-to-severe vasomotor symptoms was shown to be statistically improved compared with placebo at weeks 4 and 12. **Table 1** below shows the observed mean number of hot flushes in the CE 300 mcg, 450 mcg, and 625 mcg and placebo treatment groups over the initial 12-week period.

TABLE 1. SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY– MEAN VALUES AND COMPARISONS BETWEEN THE ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP: PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, EFFICACY EVALUABLE (EE) POPULATION

Treatment (No. of Patients)	---------- No. of Hot Flushes/Day ----------			
Time Period (week)	Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SD	p-Values vs. Placebo[a]
625 mcg CE				
4 (n=27)	12.29 ± 3.89	1.95 ± 2.77	-10.34 ± 0.90	<0.001
12(n=26)	12.03 ± 3.73	0.45 ± 0.95	-11.58 ± 0.88	<0.001
450 mcg CE				
4(n=32)	12.25 ± 5.04	5.04 ± 5.31	-7.21 ± 4.750.83	<0.001
12(n=30)	12.49 ± 5.11	2.33 ± 3.39	-10.16 ± 0.82	<0.001
300 mcg CE				
4(n=30)	13.77 ± 4.78	4.65 ± 3.71	-9.12 ± 0.85	<0.001
12(n=29)	13.83 ± 4.86	2.20 ± 2.73	-11.63 ± 0.83	<0.001
Placebo				
4(n=28)	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 0.88	-
12 (n=25)	11.61 ± 3.79	5.27 ± 4.97	-6.34 ± 0.89	-

[a]Standard errors based on assumption of equal variances.

Effects on vulvar and vaginal atrophy

Results of vaginal maturation indexes at cycles 6 and 13 showed that the differences from placebo were statistically significant ($p < 0.001$) for all treatment groups.

Effects on bone mineral density

Health and Osteoporosis, Progestin and Estrogen (HOPE) Study

The HOPE study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy post-menopausal women with an intact uterus. Subjects (mean age 53.3 ± 4.9 years) were 2.3 ± 0.9 years on average since menopause and took one 600 mg tablet of elemental calcium (Caltrate™) daily. Subjects were not given Vitamin D supplements. They were treated with CE 625 mcg, 450 mcg, 300 mcg, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L_2 to L_4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

Intent-to-treat subjects

All active treatment groups showed significant differences from placebo in each of the four BMD endpoints at cycles 6, 13, 19, and 26. The percent changes from baseline to final evaluation are shown in **Table 2** below.

TABLE 2. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LOCF

Region Evaluated Treatment Group[a]	No. of Subjects	Baseline (g/cm^2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs. Placebo
L_2 to L_4 BMD				
625	83	1.17 ± 0.15	2.32 ± 0.35	<0.001
450	91	1.13 ± 0.15	2.08 ± 0.34	<0.001
300	87	1.14 ± 0.15	1.24 ± 0.36	<0.001
Placebo	85	1.14 ± 0.14	-2.46 ± 0.35	
Total Body BMD				
625	84	1.15 ± 0.08	0.66 ± 0.17	<0.001
450	91	1.14 ± 0.08	0.71 ± 0.16	<0.001
300	87	1.14 ± 0.07	0.37 ± 0.16	<0.001
Placebo	85	1.13 ± 0.08	-1.52 ± 0.16	
Femoral Neck BMD				
625	84	0.91 ± 0.14	1.74 ± 0.43	<0.001
450	91	0.89 ± 0.13	1.95 ± 0.41	<0.001
300	87	0.86 ± 0.11	0.57 ± 0.42	<0.001
Placebo	85	0.88 ± 0.14	-1.81 ± 0.43	

TABLE 2. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LOCF

Region Evaluated Treatment Group[a]	No. of Subjects	Baseline (g/cm^2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs. Placebo
Femoral Trochanter BMD				
625	84	0.78 ± 0.13	3.78 ± 0.57	<0.001
450	91	0.76 ± 0.12	3.46 ± 0.54	0.001
300	87	0.75 ± 0.10	3.19 ± 0.55	0.003
Placebo	85	0.75 ± 0.12	0.93 ± 0.56	

[a] Identified by dosage (mcg) of CE or placebo.
BMD = Bone mineral density; L_2 to L_4 = anteroposterior lumbar spine; LOCF = Last observation carried forward; SD = Standard deviation; SE = Standard error.

The bone turnover markers serum osteocalcin and urinary N-telopeptide significantly decreased ($p < 0.001$) in all active-treatment groups at cycles 6, 13, 19, and 26 compared with the placebo group. Larger mean decreases from baseline were seen with the active groups than with the placebo group. Significant differences from placebo were seen less frequently in urine calcium.

Effects on female hypogonadism

In clinical studies of delayed puberty due to female hypogonadism, breast development was induced by doses as low as 150 mcg. The dosage may be gradually titrated upward at 6 to 12-month intervals as needed to achieve appropriate bone age advancement and eventual epiphyseal closure. Available data suggest that chronic dosing with 625 mcg is sufficient to induce artificial cyclic menses with sequential progestin treatment and to maintain bone mineral density after skeletal maturity is achieved.

Women's Health Initiative Studies (WHI)

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy post-menopausal women in two substudies to assess the risks and benefits of conjugated estrogens (CE) [625 mcg daily] alone or in combination with medroxyprogesterone acetate (MPA) [625 mcg/2.5 mg daily] compared to placebo. The primary endpoint was the incidence of coronary heart disease (CHD), i.e. non-fatal myocardial infarction (MI), silent MI and CHD death, with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the CE plus MPA

substudy), colorectal cancer, hip fracture, or death due to other causes. The study did not evaluate the effects of CE alone or CE plus MPA on menopausal symptoms.

WHI Estrogen-alone Substudy
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 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 7.1 years, are presented in **Table 3** 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 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)[27] 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.

Table 3. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI

Event	Relative Risk CE vs. Placebo (95% nCI[b])	Placebo n = 5,429	CE n = 5,310
		Absolute Risk per 10,000 Women-Years	
CHD events [c]	0.95 (0.78–1.16)	57	54
Non-fatal MI [c]	*0.91 (0.73–1.14)*	*43*	*40*
CHD death [c]	*1.01 (0.71–1.43)*	*16*	*16*
All Strokes [b]	1.33 (1.05–1.68)	33	45
Ischemic stroke[c]	*1.55 (1.19–2.01)*	*25*	*38*
Deep vein thrombosis[c,d]	1.47 (1.06–2.06)	15	23
Pulmonary embolism[c]	1.37 (0.90–2.07)	10	14

Table 3. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI

Event	Relative Risk CE vs. Placebo (95% nCI[b])	Placebo n = 5,429	CE n = 5,310
		Absolute Risk per 10,000 Women-Years	
Invasive breast cancer[c]	0.80 (0.62–1.04)	34	28
Colorectal cancer[e]	1.08 (0.75–1.55)	16	17
Hip fracture[c]	0.65 (0.45–0.94)	19	12
Vertebral fractures[c,d]	0.64 (0.44–0.93)	18	11
Lower arm/wrist fractures[c,d]	0.58 (0.47–0.72)	59	35
Total fractures[c,d]	0.71 (0.64–0.80)	197	144
Death due to other causes[e,f]	1.08 (0.88–1.32)	50	53
Overall mortality[c,d]	1.04 (0.88–1.22)	75	79
Global Index[g]	1.02 (0.92–1.13)	201	206

[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[c] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[d] Not included in global index.
[e] Results are based on an average follow-up of 6.8 years.
[f] All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.
[g] 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, colorectal cancer, hip fracture, or death due to other causes.

Table 4 describes the primary results of the Estrogen-alone substudy stratified by age at baseline.

Table 4. WOMEN'S HEALTH INITIATIVE ESTROGEN-ALONE SUBSTUDY RESULTS STRATIFIED BY AGE AT BASELINE

	AGE					
Endpoint	**50-59 years**		**60-69 years**		**70-79 years**	
	CE (N=1637)	**Placebo (N=1673)**	**CE (N=2387)**	**Placebo (N=2465)**	**CE (N=1286)**	**Placebo (N=1291)**
CHD[a,b]						
Number of cases	21	34	96	106	84	77
Absolute risk (N)[c]	17	27	58	62	98	88
Hazard ratio (95% CI)	0.63 (0.36-1.09)		0.94 (0.71-1.24)		1.13 (0.82-1.54)	
Stroke[b]						
Number of cases	18	21	84	54	66	52

Table 4. WOMEN'S HEALTH INITIATIVE ESTROGEN-ALONE SUBSTUDY RESULTS STRATIFIED BY AGE AT BASELINE

	AGE					
Endpoint	**50-59 years**		**60-69 years**		**70-79 years**	
	CE (N=1637)	**Placebo (N=1673)**	**CE (N=2387)**	**Placebo (N=2465)**	**CE (N=1286)**	**Placebo (N=1291)**
Absolute risk (N)[c]	15	17	51	31	76	59
Hazard ratio (95% CI)	0.89 (0.47-1.69)		1.62 (1.15-2.27)		1.21 (0.84-1.75)	
DVT[b]						
Number of cases	16	10	39	29	30	20
Absolute risk (N)[c]	13	8	23	17	34	22
Hazard ratio[d] (95% CI)	1.64 (0.74-3.60)		3.02 (1.51-6.06)		4.54 (2.22-9.31)	
VTE[b]						
Number of cases	20	15	54	43	37	28
Absolute risk (N)[c]	16	12	32	25	42	31
Hazard ratio[d] (95% CI)	1.37 (0.70-2.68)		2.82 (1.59-5.01)		3.77 (2.07-6.89)	
Pulmonary Embolism[b]						
Number of cases	12	8	28	17	12	14
Absolute risk (N)[c]	10	6	17	10	14	16
Hazard ratio[d] (95% CI)	1.54 (0.63-3.77)		2.80 (1.28-6.16)		2.36 (0.96-5.80)	
Invasive Breast Cancer						
Number of cases	25	35	42	60	27	29
Absolute risk (N)[c]	21	29	26	36	32	34
Hazard ratio (95% CI)	0.72 (0.43-1.21)		0.72 (0.49-1.07)		0.94 (0.56-1.60)	
Colorectal Cancer						
Number of cases	8	14	26	31	27	13
Absolute risk (N)[c]	7	12	16	19	32	15
Hazard ratio (95% CI)	0.59 (0.25-1.41)		0.88 (0.52-1.48)		2.09 (1.08-4.04)	
Hip Fracture[b]						
Number of cases	5	1	9	20	32	52
Absolute risk (N)[c]	4	1	5	12	37	58
Hazard ratio (95% CI)	5.02 (0.59-43.02)		0.47 (0.22-1.04)		0.64 (0.41-0.99)	
Total Fractures[b]						
Number of cases	153	173	220	348	167	240
Absolute risk (N)[c]	126	139	132	201	191	269
Hazard ratio (95% CI)	0.90 (0.72-1.12)		0.63 (0.53-0.75)		0.70 (0.57-0.85)	

Table 4. WOMEN'S HEALTH INITIATIVE ESTROGEN-ALONE SUBSTUDY RESULTS STRATIFIED BY AGE AT BASELINE

	AGE					
Endpoint	**50-59 years**		**60-69 years**		**70-79 years**	
	CE (N=1637)	**Placebo (N=1673)**	**CE (N=2387)**	**Placebo (N=2465)**	**CE (N=1286)**	**Placebo (N=1291)**
Overall Mortality[b]						
Number of cases	34	48	129	131	134	113
Absolute risk (N)	28	38	77	75	153	127
Hazard ratio (95% CI)	0.71 (0.46-1.11)		1.02 (0.80-1.30)		1.20 (0.93-1.55)	

[a] CHD defined as myocardial infarction or coronary death.
[b] Based on adjudicated data over a mean duration of therapy of 7.1 years.
[c] Absolute risk is per 10,000 person-years.
[d] VTE hazard ratios compared with women aged 50-59 taking placebo.

Timing of initiation of estrogen therapy from the start of menopause may affect the overall risk-benefit profile. The WHI estrogen-alone substudy stratified by age showed a non-significant trend of reduced risk for CHD and overall mortality compared with placebo in women who initiated hormone therapy closer to menopause than those initiating therapy more distant from menopause.

Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, enrolled 2,947 predominantly healthy hysterectomized post-menopausal women 65 years of age and older (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; and 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) in the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, 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 Alzheimer's disease. Since the substudy was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger post-menopausal women (see **section 4.4 Special Warnings and Precautions for Use -** *Dementia* and **section 5.1 Pharmacodynamic properties -** WHIM Study).

5.2 Pharmacokinetic Properties

Absorption
Conjugated estrogens are soluble in water and are well-absorbed from the gastrointestinal tract after release from the drug formulation. The CE tablet releases conjugated estrogens slowly over several hours. Maximum plasma concentrations are achieved approximately 6-10 hours following CE tablet administration. The estrogens are generally eliminated in near-parallel fashion with half-lives ranging from 10-20 hours, when corrected for endogenous concentrations as needed.

Distribution
The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentration in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism
Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In post-menopausal women a significant proportion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion
Estradiol, estrone, and estriol are excreted in the urine, along with glucuronide and sulfate conjugates.

Special Populations
No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

Please see outer package for the expiry date of the product.

6.2 Storage Conditions

Store at temperatures not exceeding 30°C.

6.3 Special Precautions for Disposal and Other Handling

No special requirements.

6.4 Availability

Conjugated Estrogens (Premarin) 300 mcg tablets: Green, oval, biconvex tablet, marked "0.3" in white ink; box of 1 blister strip x 28 tablets sealed in an aluminum foil laminate pouch.

Conjugated Estrogens (Premarin) 625 mcg tablets: Maroon, oval, biconvex tablet, marked "0.625" in white ink; box of 1 blister strip x 28 tablets sealed in an aluminum foil laminate pouch.

7.0 FDA REGISTRATION NUMBER

300 mcg Tablet: DR-XY21646

625 mcg Tablet: DRP-3439

8.0 DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

300 mcg Tablet: 13 July 1973

625 mcg Tablet: 06 November 1969

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
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