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 postmenopausal 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 THERAPEUTIC CATEGORY
Sex Hormones

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
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 postmenopausal osteoporosis in women at risk of future fractures.¹
4. Management of postmenopausal osteoporosis in women at risk of future fractures. Therapy should start as soon as possible after the onset of menopause.
5. 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 Special 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.

If an estrogen is prescribed for a postmenopausal woman with a uterus, the addition of a progestin may be appropriate (see section 4.4 Special Warnings and Special 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 Special Precautions for Use - Exacerbation of other conditions).

Tablets should be taken whole; do not divide, crush, chew, or dissolve tablets in mouth. Dosage adjustment may be made based on individual patient response.

Vasomotor Symptoms and/or Vulvar and Vaginal Atrophy Due to Menopause
- Consider topical vaginal products when treating solely for vulvar and vaginal atrophy.
Prevention/Management of postmenopausal osteoporosis

- Therapy should be considered for postmenopausal women at risk of future fractures and should start as soon as possible after the onset of menopause.

Female hypogonadism

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

Female castration or primary ovarian failure

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

4.3 Contraindications

1. Known, suspected or past breast cancer (except use of tablets in appropriately selected patients being treated for metastatic disease).
2. Known or suspected estrogen-dependent neoplasia (e.g. endometrial cancer, endometrial hyperplasia).
3. Known or suspected pregnancy (see section 4.6 Pregnancy and Lactation).
4. Undiagnosed abnormal uterine bleeding.
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 Special 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.2,3,4

Cardiovascular Risk
ET has been reported to increase the risk of stroke5 and deep venous thrombosis (DVT).6

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, 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 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, estrogens should be discontinued immediately (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy).

If visual abnormalities develop, discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. Retinal vascular thrombosis has been reported in patients receiving estrogens with or without progestins.7,8

If feasible, 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 Special Precautions for Use - Exacerbation of other Conditions andsection 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 postmenopausal 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 Special 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 postmenopausal 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.\textsuperscript{9}

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.

\textbf{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.

\textbf{Dementia}
The estrogen-alone arm of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI that enrolled postmenopausal 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 4.4 Special Warnings and Special Precautions for Use – Geriatric Use and section 5.1 Pharmacodynamic Properties – Clinical Efficacy).\textsuperscript{10}

It is unknown whether these findings apply to younger postmenopausal women (see section 4.4 Special Warnings and Special Precautions for Use – Geriatric Use).\textsuperscript{10}

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

\textbf{Angioedema}
Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in patients with hereditary angioedema.\textsuperscript{11,12}

\textbf{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.

\textbf{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 625 mcg, 450 mcg, and 300 mcg compared with placebo were 34.3, 30.2, 25.1, and 10.8, respectively.\textsuperscript{13}

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

\textbf{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.14,15,16

**Exacerbation of other conditions**
Estrogen replacement therapy may cause an exacerbation of asthma, epilepsy, migraine with or without aura17, otosclerosis18, 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 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 Test Interactions).

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

**Pediatric Use**
Safety and effectiveness in pediatric 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, hormonal therapy should not be started before epiphyseal closure has occurred in order not to compromise final growth.

**Geriatric Use**
There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Conjugated Estrogens (Premarin) to determine whether those over 65 years of age differ from younger subjects in their response to the medication.

*The Women’s Health Initiative Study*
In the Women’s Health Initiative (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 4.4 Special Warnings and Special Precautions for Use – *
Cardiovascular Risk and **section 5.1 Pharmacodynamic Properties – Clinical Efficacy**.

*The Women's Health Initiative Memory Study*

In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was no 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 Special Precautions for Use – Dementia** and **section 5.1 Pharmacodynamic Properties – Clinical Efficacy**).

**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 coadministered. 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 preparations (*Hypericum perforatum*), 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.

**Laboratory Test Interactions**

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII 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, decreased 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), 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 may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma HDL and HDL₂ cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.
The response to metyrapone may be reduced.

### 4.6 Pregnancy and Lactation

Estrogens should not be used during pregnancy (See section 4.3 Contraindications).

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 UNDESIRABLE EFFECTS

Adverse reactions are listed in the Table in CIOMS frequency categories:

<table>
<thead>
<tr>
<th>Frequency Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common:</td>
<td>≥ 10%</td>
</tr>
<tr>
<td>Common:</td>
<td>≥ 1 % and &lt; 10 %</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>≥ 0.1% and &lt; 1%</td>
</tr>
<tr>
<td>Rare:</td>
<td>≥ 0.01% and &lt; 0.1%</td>
</tr>
<tr>
<td>Very rare:</td>
<td>&lt; 0.01%</td>
</tr>
</tbody>
</table>

**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

4.8 Overdosage

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

MODE 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 postmenopausal 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 postmenopausal women.21

CLINICAL EFFICACY

Effects on vasomotor symptoms
In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2,805 postmenopausal 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 relief 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 adjusted 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, LAST OBSERVATION CARRIED FORWARD (LOCF)

<table>
<thead>
<tr>
<th>Treatment (No. of Patients)</th>
<th>Baseline Mean ± SD</th>
<th>Observed Mean ± SD</th>
<th>Mean Change ± SD</th>
<th>p-Values vs. Placebo&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Period (week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>625 mcg CE (n = 27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12.29 ± 3.89</td>
<td>1.95 ± 2.77</td>
<td>-10.34 ± 4.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12</td>
<td>12.29 ± 3.89</td>
<td>0.75 ± 1.82</td>
<td>-11.54 ± 4.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>450 mcg CE (n = 32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12.25 ± 5.04</td>
<td>5.04 ± 5.31</td>
<td>-7.21 ± 4.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12</td>
<td>12.25 ± 5.04</td>
<td>2.32 ± 3.32</td>
<td>-9.93 ± 4.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>300 mcg CE (n = 30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>13.77 ± 4.78</td>
<td>4.65 ± 3.71</td>
<td>-9.12 ± 4.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12</td>
<td>13.77 ± 4.78</td>
<td>2.52 ± 3.23</td>
<td>-11.25 ± 4.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo (n = 28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11.69 ± 3.87</td>
<td>7.89 ± 5.28</td>
<td>-3.80 ± 4.71</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>11.69 ± 3.87</td>
<td>5.71 ± 5.22</td>
<td>-5.98 ± 4.60</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on analysis of covariance with treatment as factor and baseline as covariate.

**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 postmenopausal 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 (L₂ to L₄). 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.²²

TABLE 2. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE INTENT-TO-MIN TREAT POPULATION, LOCF
<table>
<thead>
<tr>
<th>Region Evaluated Treatment Group&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of Subjects</th>
<th>Baseline (g/cm&lt;sup&gt;2&lt;/sup&gt;) Mean ± SD</th>
<th>Change from Baseline (%) Adjusted Mean ± SE</th>
<th>p-Value vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>L&lt;sub&gt;2&lt;/sub&gt; to L&lt;sub&gt;4&lt;/sub&gt; BMD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>625</td>
<td>83</td>
<td>1.17 ± 0.15</td>
<td>2.46 ± 0.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>450</td>
<td>91</td>
<td>1.13 ± 0.15</td>
<td>2.26 ± 0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>300</td>
<td>87</td>
<td>1.14 ± 0.15</td>
<td>1.13 ± 0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>85</td>
<td>1.14 ± 0.14</td>
<td>-2.45 ± 0.36</td>
<td></td>
</tr>
<tr>
<td><strong>Total Body BMD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>625</td>
<td>84</td>
<td>1.15 ± 0.08</td>
<td>0.68 ± 0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>450</td>
<td>91</td>
<td>1.14 ± 0.08</td>
<td>0.74 ± 0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>300</td>
<td>87</td>
<td>1.14 ± 0.07</td>
<td>0.40 ± 0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>85</td>
<td>1.13 ± 0.08</td>
<td>-1.50 ± 0.17</td>
<td></td>
</tr>
<tr>
<td><strong>Femoral Neck BMD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>625</td>
<td>84</td>
<td>0.91 ± 0.14</td>
<td>1.82 ± 0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>450</td>
<td>91</td>
<td>0.89 ± 0.13</td>
<td>1.84 ± 0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>300</td>
<td>87</td>
<td>0.86 ± 0.11</td>
<td>0.62 ± 0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>85</td>
<td>0.88 ± 0.14</td>
<td>-1.72 ± 0.45</td>
<td></td>
</tr>
<tr>
<td><strong>Femoral Trochanter BMD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>625</td>
<td>84</td>
<td>0.78 ± 0.13</td>
<td>3.82 ± 0.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>450</td>
<td>91</td>
<td>0.76 ± 0.12</td>
<td>3.16 ± 0.56</td>
<td>0.003</td>
</tr>
<tr>
<td>300</td>
<td>87</td>
<td>0.75 ± 0.10</td>
<td>3.05 ± 0.57</td>
<td>0.005</td>
</tr>
<tr>
<td>Placebo</td>
<td>85</td>
<td>0.75 ± 0.12</td>
<td>0.81 ± 0.58</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Identified by dosage (mcg) of CE or placebo.

**Figure 1** below shows the cumulative percentage of subjects with changes from baseline equal to or greater than the value shown on the x-axis.
Figure 1. CUMULATIVE PERCENT OF SUBJECTS WITH CHANGES FROM BASELINE IN SPINE BMD OF GIVEN MAGNITUDE OR GREATER IN CE AND PLACEBO GROUPS

The mean percent changes from baseline in L2 to L4 BMD for women who completed the bone density study are shown with standard error bars by treatment group in Figure 2 below. Significant differences between each of the CE dosage groups and placebo were found at cycles 6, 13, 19, and 26.
Figure 2. ADJUSTED MEAN (SE) PERCENT CHANGE FROM BASELINE AT EACH CYCLE IN SPINE BMD: SUBJECTS COMPLETING IN CE GROUPS AND PLACEBO

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.23,24

Women’s Health Initiative Studies (WHI)
The Women’s Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal 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/2.5mg daily] compared to placebo. The primary endpoint was the incidence of coronary heart disease (CHD), i.e. nonfatal 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)25; 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), respectively26. 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.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE vs. Placebo (95% nCI)</th>
<th>Placebo n = 5,429</th>
<th>CE n = 5,310</th>
<th>Absolute Risk per 10,000 Women-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events c</td>
<td>0.95 (0.78–1.16)</td>
<td>57</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI c</td>
<td>0.91 (0.73–1.14)</td>
<td>43</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>CHD death c</td>
<td>1.01 (0.71–1.43)</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>All Strokes b</td>
<td>1.33 (1.05–1.68)</td>
<td>33</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke c</td>
<td>1.55 (1.19–2.01)</td>
<td>25</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis c,d</td>
<td>1.47 (1.06–2.06)</td>
<td>15</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism c</td>
<td>1.37 (0.90–2.07)</td>
<td>10</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Invasive breast cancer e</td>
<td>0.80 (0.62–1.04)</td>
<td>34</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer e</td>
<td>1.08 (0.75–1.55)</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Hip fracture c</td>
<td>0.65 (0.45–0.94)</td>
<td>19</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Vertebral fractures c,d</td>
<td>0.64 (0.44–0.93)</td>
<td>18</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Lower arm/wrist fractures c,d</td>
<td>0.58 (0.47–0.72)</td>
<td>59</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Total fractures c,d</td>
<td>0.71 (0.64–0.80)</td>
<td>197</td>
<td>144</td>
<td></td>
</tr>
<tr>
<td>Death due to other causes e,f</td>
<td>1.08 (0.88–1.32)</td>
<td>50</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Overall mortality c,d</td>
<td>1.04 (0.88–1.22)</td>
<td>75</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Global Index g</td>
<td>1.02 (0.92–1.13)</td>
<td>201</td>
<td>206</td>
<td></td>
</tr>
</tbody>
</table>

a Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

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 below describes the primary results of the Estrogen-alone substudy stratified by age at baseline.
<table>
<thead>
<tr>
<th>AGE</th>
<th>Endpoint</th>
<th>50-59 years</th>
<th>60-69 years</th>
<th>70-79 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CE (N=1637)</td>
<td>Placebo (N=1673)</td>
<td>CE (N=2387)</td>
</tr>
<tr>
<td></td>
<td>CHD(^{a,b})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>21</td>
<td>34</td>
<td>96</td>
<td>106</td>
</tr>
<tr>
<td>Absolute risk (N) (^c)</td>
<td>17</td>
<td>27</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.63 (0.36-1.09)</td>
<td>0.94 (0.71-1.24)</td>
<td>1.13 (0.82-1.54)</td>
<td></td>
</tr>
<tr>
<td>Stroke(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>18</td>
<td>21</td>
<td>84</td>
<td>54</td>
</tr>
<tr>
<td>Absolute risk (N) (^c)</td>
<td>15</td>
<td>17</td>
<td>51</td>
<td>31</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.89 (0.47-1.69)</td>
<td>1.62 (1.15-2.27)</td>
<td>1.21 (0.84-1.75)</td>
<td></td>
</tr>
<tr>
<td>DVT(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>16</td>
<td>10</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>Absolute risk (N) (^c)</td>
<td>13</td>
<td>8</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.64 (0.74-3.60)</td>
<td>3.02 (1.51-6.06)</td>
<td>4.54 (2.22-9.31)</td>
<td></td>
</tr>
<tr>
<td>VTE (^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>20</td>
<td>15</td>
<td>54</td>
<td>43</td>
</tr>
<tr>
<td>Absolute risk (N) (^c)</td>
<td>16</td>
<td>12</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.37 (0.70-2.68)</td>
<td>2.82 (1.59-5.01)</td>
<td>3.77 (2.07-6.89)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Embolism(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>12</td>
<td>8</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>Absolute risk (N) (^c)</td>
<td>10</td>
<td>6</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.54 (0.63-3.77)</td>
<td>2.80 (1.28-6.16)</td>
<td>2.36 (0.96-5.80)</td>
<td></td>
</tr>
<tr>
<td>Invasive Breast Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>25</td>
<td>35</td>
<td>42</td>
<td>60</td>
</tr>
<tr>
<td>Absolute risk (N) (^c)</td>
<td>21</td>
<td>29</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.72 (0.43-1.21)</td>
<td>0.72 (0.49-1.07)</td>
<td>0.94 (0.56-1.60)</td>
<td></td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>8</td>
<td>14</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Absolute risk (N) (^c)</td>
<td>7</td>
<td>12</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.59 (0.25-1.41)</td>
<td>0.88 (0.52-1.48)</td>
<td>2.09 (1.08-4.04)</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. WOMEN’S HEALTH INITIATIVE ESTROGEN-ALONE SUBSTUDY RESULTS STRATIFIED BY AGE AT BASELINE

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>50-59 years</th>
<th></th>
<th>60-69 years</th>
<th></th>
<th>70-79 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CE (N=1637)</td>
<td>Placebo (N=1673)</td>
<td>CE (N=2387)</td>
<td>Placebo (N=2465)</td>
<td>CE (N=1286)</td>
<td>Placebo (N=1291)</td>
</tr>
<tr>
<td><strong>Hip Fracture</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>5</td>
<td>1</td>
<td>9</td>
<td>20</td>
<td>32</td>
<td>52</td>
</tr>
<tr>
<td>Absolute risk (N)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>12</td>
<td>37</td>
<td>58</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>5.02 (0.59-43.02)</td>
<td></td>
<td>0.47 (0.22-1.04)</td>
<td></td>
<td>0.64 (0.41-0.99)</td>
<td></td>
</tr>
<tr>
<td><strong>Total Fractures</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>153</td>
<td>173</td>
<td>220</td>
<td>348</td>
<td>167</td>
<td>240</td>
</tr>
<tr>
<td>Absolute risk (N)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>126</td>
<td>139</td>
<td>132</td>
<td>201</td>
<td>191</td>
<td>269</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.90 (0.72-1.12)</td>
<td></td>
<td>0.63 (0.53-0.75)</td>
<td></td>
<td>0.70 (0.57-0.85)</td>
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</tr>
<tr>
<td><strong>Overall Mortality</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>34</td>
<td>48</td>
<td>129</td>
<td>131</td>
<td>134</td>
<td>113</td>
</tr>
<tr>
<td>Absolute risk (N)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>28</td>
<td>38</td>
<td>77</td>
<td>75</td>
<td>153</td>
<td>127</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.71 (0.46-1.11)</td>
<td></td>
<td>1.02 (0.80-1.30)</td>
<td></td>
<td>1.20 (0.93-1.55)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> CHD defined as myocardial infarction or coronary death

<sup>b</sup> Based on adjudicated data over a mean duration of therapy of 7.1 years

<sup>c</sup> Absolute risk is per 10,000 person-years.

<sup>d</sup> 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 postmenopausal 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 postmenopausal women (see section 4.4 Special Warnings and Special Precautions for Use – Dementia and section 4.4 Special Warnings and Precautions for Use – Geriatric Use).
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.29

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 postmenopausal 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.29

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
Store at temperatures not exceeding 30°C

6.3 Instructions for Use and Handling
No special requirements.

6.4 Availability
Conjugated Estrogens (Premarin) 300 mcg tablets: Green, oval, biconvex tablet,
marked “0.3” in white ink; in box of 1 blister strip x 28 tablets.

**Conjugated Estrogens (Premarin) 625 mcg tablets:** Maroon, oval, biconvex tablet, marked “0.625” in white ink; in box of 1 blister strip x 28 tablets.

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

**KEEP OUT OF REACH OF CHILDREN**

Manufactured by:
**PFIZER IRELAND PHARMACEUTICALS**
Newbridge, Co. Kildare, Ireland

Imported by:
**PFIZER, INC.**
23/F Ayala Life-FGU Center
6811 Ayala Avenue, Makati City
Philippines

Under Authority of PFIZER, INC., New York, NY, USA

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Revision no: 1.0  
Revision date: 9 June 2011  
Reference: CDS 26.0/Amended CPR  
Reference date: 11 May 2011/ 9 June 2011
References


