Premarin®
(conjugated estrogens)

پریمیرین®

0.3mg

Tablets

DESCRIPTION

PREMARIN® *(conjugated estrogens tablets) for oral administration contains a mixture of conjugated estrogens obtained exclusively from natural sources.*

INDICATIONS

Treatment of moderate to severe vasomotor symptoms associated with the menopause.

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

Prevention of postmenopausal osteoporosis.
Prevention of postmenopausal osteoporosis in women at risk of future fractures.

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

Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).

DOSAGE AND ADMINISTRATION

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, Malignant neoplasms). In some cases, hysterectomized women with a history of endometriosis may need a progestin (see Section, 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

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

Prevention 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).

Breast cancer (for palliation only)

- 10mg three times daily, for a period of at least three months.

Advanced androgen-dependent carcinoma of the prostate (for palliation only)

- 1.25mg to 2.5 mg three times daily.

CONTRAINDICATIONS

- Known or suspected pregnancy (see section, pregnancy).
- Undiagnosed abnormal uterine bleeding.
- Known, suspected, or past breast cancer (except use of tablets in appropriately selected patients being treated for metastatic disease).
- Known or suspected estrogen-dependent neoplasia (e.g., endometrial cancer, endometrial hyperplasia).
- Active or history of arterial thromboembolic disease (e.g., stroke, myocardial infarction) or venous thromboembolism (such as deep venous thrombosis, pulmonary embolism).
- Active or chronic liver dysfunction or disease.
- Known or suspected hypersensitivity to ingredients.

SPECIAL WARNINGS

General

Combined Estrogen and Progestin Therapy:

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

ERT 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.

Stroke

In the estrogen-alone substudy of the WHI, a statistically significant increased risk of stroke was reported in women receiving estrogen alone compared with women receiving placebo (45 vs. 33 per 10,000 person-years). The increase in risk was observed during year one and persisted. Should a stroke occur or be suspected, estrogens should be discontinued immediately (see section, pharmacodynamics, 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, pharmacodynamics, clinical efficacy).

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, EXACERBATION OF OTHER CONDITIONS and section, pharmacodynamics, 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 to 15 years after ERT 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, 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, PHARMACODYNAMICS, EFFICACY). In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer.

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

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 (see section, GERIATRIC USE, and section PHARMACODYNAMICS, CLINICAL EFFICACY).

Gallbladder disease

A 2- to 4-fold increase in the risk of gallbladder disease requiringsurgery in women receiving ERT has been reported.

Visual abnormalities

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

Hypercalcemia

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Palliative therapy in men

Large doses of estrogen (5 mg conjugated equine estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

PRECAUTIONS

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 0.625mg, 0.45mg, and 0.3mg compared with placebo were 34.3,30.2, 25.1, and 10.7, respectively.

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.

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.

Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure during ERT have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial a generalized effect of ERT on blood pressure was not seen.

Exacerbation of other conditions

Estrogen replacement therapy may cause an exacerbation of asthma, epilepsy, migraine, diabetes mellitus with or without vascular involvement, 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 ERT. Addition of a progestin should be considered in women who have undergone hysterectomy but are known to have residual endometriosis, since malignant transformation after estrogen-only therapy has been reported.

Hypocalcemia

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

Hypothyroidism

Patients dependent on thyroid hormone replacement therapy may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range (see section, Laboratory test interactions).

Laboratory monitoring

Estrogen administration should be guided by clinical response rather than by hormone levels (eg, estradiol, FSH).

PREGNANCY

Estrogens should not be used during pregnancy (see section, CONTRAINDICATIONS).

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.

PEDIATRIC USE

Clinical studies have not been conducted in the pediatric population. Although estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay, safety and effectiveness in pediatric patients have not otherwise 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

The estrogen-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 section, Cardiovascular risk and section, Pharmacodynamics, clinical efficacy).

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 (see section, Dementia and section, pharmacodynamics, clinical efficacy).

INTERACTIONS

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.

INTERFERENCE WITH LABORATORY AND OTHER DIAGNOSTIC TESTS

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), 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, ie, 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 HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

The response to metyrapone may be reduced.

Adverse Reactions

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	Arthralagias; 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 disorders	
Uncommon	Gallbladder disease.
Very rare	Cholestatic jaundice.
General disorders and administration site conditions	
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.
Investigations	
Common	Changes in weight (increase or decrease) Increased triglycerides.
Very rare	Increases in blood pressure.

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.

MODE OF ACTION

Estrogens generally 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.

PHARMACODYNAMICS, 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 (0.3mg, 0.45mg, and 0.625mg 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 below shows the adjusted mean number of hot flushes in the CE 0.3mg, 0.45mg, and 0.625mg and placebo treatment groups over the initial 12-week period.

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)

Treatment (No. of Patients)	No. of Hot Flushes/Day			
Time Period (week)	Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SD	p-Value vs Placebo[a]
0.625mg CE (n = 27)				
4	12.29 ± 3.89	1.95 ± 2.77	-10.34 ± 4.73	<0.001
12	12.29 ± 3.89	0.75 ± 1.82	-11.54 ± 4.62	<0.001
0.45mg CE (n = 32)				
4	12.25 ± 5.04	5.04 ± 5.31	-7.21 ± 4.75	<0.001
12	12.25 ± 5.04	2.32 ± 3.32	-9.93 ± 4.64	<0.001
0.3mg CE (n = 30)				
4	13.77 ±4.78	4.65 ± 3.71	-9.12 ± 4.71	<0.001
12	13.77 ± 4.78	2.52 ± 3.23	-11.25 ± 4.60	<0.001
Placebo (n = 28)				
4	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 4.71	-
12	11.69 ± 3.87	5.71 ± 5.22	-5.98 ± 4.60	-

a: Based on analysis of covariance with treatment as factor & 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 0.625 mg, 0.45 mg, 0.3 mg, 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 the following table.

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/cm2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs Placebo
L2 to L4 BMD				
0.625	83	1.17 ± 0.15	2.46 ± 0.37	<0.001
0.45	91	1.13 ± 0.15	2.26 ± 0.35	<0.001
0.3	87	1.14 ± 0.15	1.13 ± 0.36	<0.001
Placebo	85	1.14 ± 0.14	-2.45 ± 0.36	
Total Body BMD				
0.625	84	1.15 ± 0.08	0.68 ± 0.17	<0.001
0.45	91	1.14 ± 0.08	0.74 ± 0.16	<0.001
0.3	87	1.14 ± 0.07	0.40 ± 0.17	<0.001
Placebo	85	1.13 ± 0.08	-1.50 ± 0.17	
Femoral Neck BMD				
0.625	84	0.91 ± 0.14	1.82 ± 0.45	<0.001
0.45	91	0.89 ± 0.13	1.84 ± 0.44	<0.001
0.3	87	0.86 ± 0.11	0.62 ± 0.45	<0.001
Placebo	85	0.88 ± 0.14	-1.72 ± 0.45	
Femoral Trochanter BMD				
0.625	84	0.78 ± 0.13	3.82 ± 0.58	<0.001
0.45	91	0.76 ± 0.12	3.16 ± 0.56	0.003
0.3	87	0.75 ± 0.10	3.05 ± 0.57	0.005
Placebo	85	0.75 ± 0.12	0.81 ± 0.58	

a: Identified by dosage (mg) of CEE or placebo.

Effects on female hypogonadism

In clinical studies of delayed puberty due to female hypogonadism, breast development was induced by doses as low as 0.15Êmg. 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 0.625mg 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 postmenopausal women in two substudies to assess the risks and benefits of conjugated estrogens (CE) [0.625 mg daily] alone or in combination with medroxyprogesterone acetate (MPA) [0.625Êmg/2.5 mg daily] compared to placebo. The primary endpoint was the incidence of coronary heart disease (CHD), i.e. nonfatal myocardial infarction (MI), silent MI and coronary death. The primary safety endpoint was incidence of invasive breast cancer. The substudy did not evaluate the effects of hormone replacement therapy on menopausal symptoms.

The estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints.

No overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or death, due to CHD) was reported in women receiving estrogen alone compared with placebo. Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other), after an average follow-up of 6.8 years, are presented in the table below.

In the estrogen-alone substudy of WHI, there was no significant overall effect on the relative risk (RR) of CHD (RR 0.95, 95% nominal confidence interval [nCI] 0.79-1.16); 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 1.37, 95% nCI 1.09-1.73) 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), (RRÊ0.64,Ê95%ÊnCI 0.44-0.93), and (RR 0.71, 95% nCI 0.64-0.80), respectively. The estrogen-alone substudy did not report a statistically significant effect on death due to other causes (RR 1.08, 95% nCI 0.88-1.32) or an effect on overall mortality risk (RRÊ1.04,Ê95%ÊnCIÊ0.88-1.22). These confidence intervals are unadjusted for multiple looks and multiple comparisons.

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

Event	Relative Risk CE vs. placebo (95% nCI[a])	Placebo n = 5,429	CE n = 5,310
		Absolute Risk per 10,000 Women-years	
CHD events[b],	0.95 (0.78-1.16)	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
All Stroke[b],	1.33 (1.05-1.68)	33	45
Ischemic[b]	1.55 (1.19-2.01)	25	38
Deep vein thrombosis[b,c],	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[d],	1.08 (0.75-1.55)	16	17
Hip fracture[b],	0.65 (0.45-0.94)	19	12
Vertebral fractures[b,c],	0.64 (0.44-0.93)	18	11
Lower arm/wrist fractures[b,c]	0.58 (0.47-0.72)	59	35
Total fractures[b,c],	0.71 (0.64-0.80)	197	144
Death due to other causes[d,e],	1.08 (0.88-1.32)	50	53
Overall mortality[b,c],	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 Not included in global index.

d Results are based on an average follow-up of 6.8 years.

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, colorectal cancer, hip fracture, or death due to other causes.

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

Women's Health Initiative Estrogen-alone Substudy Results Stratified by Age at Baseline

Endpoint	AGE 50-59 years		60-69 years		70-79 years	
	CEE (N=1637)	Placebo (N=1673)	CEE (N=2387)	Placebo (N=2465)	CEE (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
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 ratiod (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)	
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 nonsignificant trend of reduced risk for CHD and Total 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

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 2,947 predominantly healthy hysterectomized postmenopausal women aged 65 to 79 years was randomized to conjugated estrogens (CE) (0.625Êmg daily) or placebo. The relative risk of probable dementia for CE alone vs. placebo was 1.49Ê(95%ÊCIÊ0.83-2.66). 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 both the treatment and placebo groups was AD. 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, Dementia and section GERIATRIC USE).

AVAILABILITY

Blisters strips of 30's packed in a carton with direction circular.

STORAGE AND SHELF LIFE

Protect from heat and moisture, and shelf life is 3 years.

Rev.April, 2010

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