Premarin®
Intravenous

(conjugated estrogens, USP) for injection

Specially prepared for Intravenous & Intramuscular use

Rx only

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 doses. (See **WARNINGS**, **Malignant neoplasms**, ***Endometrial cancer***.)

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS**, **Cardiovascular disorders** and **Dementia**.)

The estrogen-alone substudy of the Women's Health Initiative (WHI) reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) per day relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS**, **Cardiovascular disorders**.)

The estrogen-plus-progestin substudy of the WHI reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS**, **Cardiovascular disorders** and **Malignant neoplasms**, ***Breast cancer***.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with CE 0.625 mg alone and during four years of treatment with CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS**, **Dementia** and **PRECAUTIONS**, **Geriatric Use**.)

Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins, were not studied in the WHI clinical trials, and in the absence of comparable data, these risks 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.

DESCRIPTION

Premarin® Intravenous (conjugated estrogens, USP) for injection contains a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of materials derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin.

Each Secule® vial contains 25 mg of conjugated estrogens, USP, in a sterile lyophilized cake which also contains lactose 200 mg, sodium citrate 12.2 mg, and simethicone 0.2 mg. The pH is adjusted with sodium hydroxide or hydrochloric acid. A sterile diluent (5 mL) containing 2% benzyl alcohol in sterile water is provided for reconstitution. The reconstituted solution is suitable for intravenous or intramuscular injection.

CLINICAL PHARMACOLOGY

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, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogen 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.

Pharmacokinetics

A. Absorption

Conjugated estrogens are soluble in water and are well-absorbed through the skin, mucous membranes, and gastrointestinal tract after release from the drug formulation.

B. 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.

C. 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.

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

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

F. Drug Interactions
Data from a single-dose drug-drug interaction study involving oral conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic dispositions of both drugs are not altered when the drugs are coadministered. No other clinical drug-drug interaction studies have 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, carbamazepine, and rifampin, 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 erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

CLINICAL STUDIES
Women's Health Initiative Studies
The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of oral conjugated estrogens (CE 0.625 mg) alone or in combination with medroxyprogesterone acetate (CE 0.625 mg/MPA 2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (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 CE/MPA), colorectal cancer, hip fracture, or death due to other causes. The study did not evaluate the effects of CE or CE/MPA 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. 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 Table 1 below.

TABLE 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI

Event	Relative Risk CE vs. Placebo (95% nCI[a])	CE n=5,310	Placebo n=5,429
		Absolute Risk per 10,000 Women-years	
CHD events[b]	0.95 (0.79-1.16)	53	56
Non-fatal MI[b]	*0.91 (0.73-1.14)*	*40*	*43*
CHD death[b]	*1.01 (0.71-1.43)*	*16*	*16*
Stroke[c]	1.39 (1.10-1.77)	44	32
Deep vein thrombosis[b,d]	1.47 (1.06-2.06)	23	15
Pulmonary embolism[b]	1.37 (0.90-2.07)	14	10
Invasive breast cancer[b]	0.80 (0.62-1.04)	28	34
Colorectal cancer[c]	1.08 (0.75-1.55)	17	16
Hip fracture[c]	0.61 (0.41-0.91)	11	17
Vertebral fractures[c,d]	0.62 (0.42-0.93)	11	17
Total fractures[c,d]	0.70 (0.63-0.79)	139	195
Death due to other causes[c,e]	1.08 (0.88-1.32)	53	50
Overall mortality[c,d]	1.04 (0.88-1.22)	81	78
Global Index[c,f]	1.01 (0.91-1.12)	192	190

[a]Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[b]Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[c]Results are based on an average follow-up of 6.8 years.
[d]Not included in Global Index.
[e]All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.
[f]A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE alone were 12 more strokes while the absolute risk reduction per 10,000 women-years was six fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant two events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Final adjudicated results for CHD events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) in women receiving CE alone compared with placebo (see Table 1).

The estrogen-plus-progestin substudy was also stopped early. According to the predefined stopping rule, after an average follow-up of 5.2 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years (RR 1.15, 95% nCI 1.03-1.28).

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were six more CHD events, seven more strokes, ten more PEs, and eight more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were seven fewer colorectal cancers and five fewer hip fractures. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Results of the estrogen-plus-progestin substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.8% Black, 5.4% Hispanic, 3.9% Other) are presented in Table 2 below. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

TABLE 2. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-PLUS-PROGESTIN SUBSTUDY OF WHI AT 5.6 YEARS[a]

Event	Relative Risk CE/MPA vs. Placebo at 5.6 Years (95% nCI[b])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-years	
CHD events	1.24 (1.00-1.54)	39	33
Non-fatal MI	*1.28 (1.00-1.63)*	*31*	*25*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All strokes	1.31 (1.02-1.68)	31	24
Ischemic stroke	*1.44 (1.09-1.90)*	*26*	*18*
Deep vein thrombosis	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer[c]	1.24 (1.01-1.54)	41	33
Invasive colorectal cancer	0.56 (0.38-0.81)	9	16
Endometrial cancer	0.81 (0.48-1.36)	6	7
Cervical cancer	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures	0.71 (0.59-0.85)	44	62
Total fractures	0.76 (0.69-0.83)	152	199

[a]Results are based on centrally adjudicated data. Mortality data was not part of the adjudicated data, however data at 5.2 years of follow-up showed no difference between the groups in terms of all-cause mortality (RR 0.98, 95% nCI 0.82-1.18).
[b]Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[c]Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.

Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45%, age 65 to 69 years; 36%, 70 to 74 years; 19%, 75 years of age and older) to evaluate the effects of CE 0.625 mg daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen-alone group was 1.49 (95% CI 0.83-2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS**, **WARNINGS**, **Dementia** and **PRECAUTIONS**, **Geriatric Use**.)

The estrogen-plus-progestin WHIMS substudy enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47%, age 65 to 69 years; 35%, 70 to 74 years; 18%, 75 years of age and older) to evaluate the effects of CE/MPA 0.625 mg conjugated estrogens/2.5 mg medroxyprogesterone acetate daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of four years, 40 women in the estrogen-plus-progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI 1.21-3.48) compared to placebo.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS**, **WARNINGS**, **Dementia** and **PRECAUTIONS**, **Geriatric Use**.)

INDICATIONS AND USAGE
Premarin Intravenous (conjugated estrogens, USP) for injection is indicated in the treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology.

Premarin Intravenous is indicated for short-term use only, to provide a rapid and temporary increase in estrogen levels.

CONTRAINDICATIONS
Premarin Intravenous should not be used in individuals with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.

2. Known, suspected, or history of cancer of the breast.

3. Known or suspected estrogen-dependent neoplasia.

4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.

5. Active or recent (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).

6. Liver dysfunction or disease.

7. Premarin Intravenous for injection should not be used in patients with known hypersensitivity to its ingredients.

8. Known or suspected pregnancy. There is no indication for Premarin Intravenous in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogen and progestins from oral contraceptives inadvertently during pregnancy. (See **PRECAUTIONS**.)

WARNINGS
See **BOXED WARNINGS.**

Premarin Intravenous is indicated for short-term use. However, warnings, precautions and adverse reactions associated with Premarin tablets should be taken into account.

1. **Cardiovascular disorders**

Estrogen-alone therapy has been associated with an increased risk of stroke and deep vein thrombosis (DVT).

Estrogen-plus-progestin therapy has been associated with an increased risk of myocardial infarction as well as stroke, venous thrombosis and pulmonary embolism.

Should any of these events occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. ***Stroke***

In the estrogen-alone substudy of the Women's Health Initiative (WHI) study, a statistically significant increased risk of stroke was reported in women receiving CE 0.625 mg daily compared to women receiving placebo (44 vs. 32 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, a statistically significant increased risk of stroke was reported in women receiving CE/MPA 0.625 mg/2.5 mg daily compared to women receiving placebo (31 vs. 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted.

b. ***Coronary heart disease***

In the estrogen-alone substudy of WHI, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or death, due to CHD) was reported in women receiving estrogen alone compared to placebo. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, no statistically significant increase of CHD events was reported in women receiving CE/MPA compared to women receiving placebo (39 vs. 33 per 10,000 women-years). An increase in relative risk was demonstrated in year one, and a trend toward decreasing relative risk was reported in years 2 through 5.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with CE/MPA 0.625 mg conjugated estrogens/2.5 mg medroxyprogesterone acetate daily demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year one, but not during the subsequent years. Two thousand three hundred and twenty-one women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in the HERS, the HERS II, and overall.

Large doses of estrogen (5 mg conjugated 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.

c. ***Venous thromboembolism (VTE)***

In the estrogen-alone substudy of WHI, the risk of VTE (DVT and pulmonary embolism [PE]), was reported to be increased for women taking conjugated estrogens (30 vs. 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 vs. 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first two years. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, a statistically significant 2-fold greater rate of VTE was reported in women receiving CE/MPA compared to women receiving placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and PE (18 vs. 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted.

2. **Malignant neoplasms**

a. ***Endometrial cancer***

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

b. ***Breast cancer***

In some studies, the use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) (see **CLINICAL STUDIES**). The results from observational studies are generally consistent with those of the WHI clinical trial.

Observational studies have also reported an increased risk of breast cancer for estrogen-plus-progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen-plus-progestin combination therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen-plus-progestin combinations, doses, or routes of administration.

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 (RR 0.80, 95% nCI 0.62-1.04).

In the estrogen-plus-progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer. In this substudy, prior use of estrogen alone or estrogen-plus-progestin combination hormone therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24 (95% nCI 1.01-1.54), and the absolute risk was 41 vs. 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo, respectively. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen-plus-progestin group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

3. **Dementia**

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to CE (0.625 mg daily) or placebo. In the estrogen-plus-progestin WHIMS substudy, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo.

In the estrogen-alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. 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.

In the estrogen-plus-progestin substudy, after an average follow-up of four years, 40 women in the estrogen-plus-progestin group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestin vs. placebo was 2.05 (95% CI 1.21-3.48). The absolute risk of probable dementia for CE/MPA vs. placebo was 45 vs. 22 cases per 10,000 women-years.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **PRECAUTIONS**, **Geriatric Use**.)

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

5. **Hypercalcemia**
   Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. **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, estrogens should be discontinued.

PRECAUTIONS

A. General

Premarin Intravenous is indicated for short-term use. However, warnings, precautions and adverse reactions associated with Premarin tablets should be taken into account.

1. ***Addition of a progestin when a woman has not had a hysterectomy***

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks which may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance.

2. ***Elevated blood pressure***

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

3. ***Hypertriglyceridemia***

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. ***Impaired liver function and past history of cholestatic jaundice***

Estrogens may be poorly metabolized in patients with impaired liver function. 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.

5. ***Hypothyroidism***
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. ***Fluid retention***
Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. ***Hypocalcemia***
Estrogens should be used with caution in individuals with severe hypocalcemia.

8. ***Ovarian cancer***
The estrogen-plus-progestin substudy of WHI reported that after an average follow-up of 5.6 years, the relative risk of ovarian cancer for estrogen plus progestin vs. placebo was 1.58 (95% nCI 0.77 – 3.24) but was not statistically significant. The absolute risk for estrogen plus progestin vs. placebo was 4.2 vs. 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

9. ***Exacerbation of endometriosis***
Endometriosis may be exacerbated with administration of estrogen therapy.

Malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

10. ***Exacerbation of other conditions***
Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

B. Patient Information
Physicians are advised to discuss the contents of the **PATIENT INFORMATION** leaflet with patients who are being treated with Premarin Intravenous.

C. Laboratory Tests
Estrogen administration should be guided by clinical response at the lowest dose, rather than laboratory monitoring.

D. Drug/Laboratory Test Interactions

1. 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.

2. Increased 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. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

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

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, and Impairment of Fertility

(See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

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

F. Pregnancy

Premarin Intravenous should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

G. Nursing Mothers

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 Premarin Intravenous is administered to a nursing woman.

H. Pediatric Use

Estrogen 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.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding. In boys, estrogen treatment may modify the normal pubertal process and induce gynecomastia. (See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**.)

I. Geriatric Use

Of the total number of subjects in the estrogen-alone substudy of the Women's Health Initiative (WHI) study, 46% (n=4,943) were 65 years and over, while 7.1% (n=767) were 75 years and over. There was a higher relative risk (CE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over.

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg daily) or placebo. After an average follow-up of 5.2 years, the relative risk (CE vs. placebo) of probable dementia was 1.49 (95% CI 0.83-2.66). The absolute risk of developing probable dementia with estrogen alone was 37 vs. 25 cases per 10,000 women-years with placebo.

Of the total number of subjects in the estrogen-plus-progestin substudy of the Women's Health Initiative study, 44% (n=7,320) were 65-74 years of age, while 6.6% (n=1,095) were 75 years and over. There was a higher relative risk (CE/MPA vs. placebo) of non-fatal stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen-plus-progestin combination group compared to the placebo group was 75 vs. 24 per 10,000 women-years and 52 vs. 12 per 10,000 women-years, respectively.

In the estrogen-plus-progestin WHIMS substudy, a population of 4,532 postmenopausal women, aged 65 to 79 years, was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo. In the estrogen-plus-progestin group, after an average follow-up of four years, the relative risk (CE/MPA vs. placebo) of probable dementia was 2.05 (95% CI 1.21-3.48). The absolute risk of developing probable dementia with CE/MPA was 45 vs. 22 cases per 10,000 women-years with placebo.

Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer's disease.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS**, **Dementia**.)

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

ADVERSE REACTIONS

See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.

Premarin Intravenous is indicated for short-term use. However, the warnings, precautions and adverse reactions associated with Premarin tablets should be taken into account.

1. *Genitourinary system.*
   Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting.
   Increase in size of uterine leiomyomata.
   Vaginal candidiasis.
   Change in amount of cervical secretion.
   Ovarian cancer.
   Endometrial hyperplasia.
   Endometrial cancer.

2. *Breasts.*
   Pain, tenderness, enlargement.
   Breast cancer.

3. *Cardiovascular.*
   Deep and superficial venous thrombosis.
   Pulmonary embolism.
   Thrombophlebitis.
   Hypotension.
   Myocardial infarction.
   Stroke.

4. *Gastrointestinal.*
   Nausea, vomiting.
   Abdominal cramps, bloating.
   Cholestatic jaundice.
   Increased incidence of gallbladder disease.
   Pancreatitis.
   Enlargement of hepatic hemangiomas.

5. *Skin.*
   Chloasma or melasma that may persist when drug is discontinued.
   Erythema multiforme.
   Erythema nodosum.
   Hemorrhagic eruption.
   Loss of scalp hair.
   Hirsutism.
   Pruritis.
   Rash.

6. *Eyes.*
   Retinal vascular thrombosis.
   Intolerance to contact lenses.

7. *Central Nervous System.*
   Headache.
   Migraine.
   Dizziness.
   Mental depression.
   Chorea.
   Nervousness.
   Exacerbation of epilepsy.
   Dementia.

8. *Miscellaneous.*
   Increase or decrease in weight.
   Reduced carbohydrate tolerance.
   Aggravation of porphyria.
   Edema.
   Changes in libido.
   Anaphylactoid/anaphylactic reactions.
   Urticaria.
   Angioedema.
   Injection site pain.
   Injection site edema.
   Phlebitis (injection site).
   Exacerbation of asthma.
   Increased triglycerides.

OVERDOSAGE
Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION
For treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology:

One 25 mg injection, intravenously or intramuscularly. Intravenous use is preferred since more rapid response can be expected from this mode of administration. Repeat in 6 to 12 hours if necessary. The use of Premarin Intravenous for injection does not preclude the advisability of other appropriate measures.

One should adhere to the usual precautionary measures governing intravenous administration. Injection should be made SLOWLY to obviate the occurrence of flushes.

Infusion of Premarin Intravenous for injection with other agents is not generally recommended. In emergencies, however, when an infusion has already been started it may be expedient to make the injection into the tubing just distal to the infusion needle. If so used, compatibility of solutions must be considered.

COMPATIBILITY OF SOLUTIONS: Premarin Intravenous is compatible with normal saline, dextrose, and invert sugar solutions. **It is not compatible with protein hydrolysate, ascorbic acid, or any solution with an acid pH.**

DIRECTIONS FOR STORAGE AND RECONSTITUTION
STORAGE BEFORE RECONSTITUTION: Store package in refrigerator, 2° to 8°C (36° to 46°F).

TO RECONSTITUTE: First withdraw air from Secule® vial so as to facilitate introduction of sterile diluent. Then, flow the sterile diluent slowly against the side of Secule® vial and agitate gently. **Do not shake violently.**

STORAGE AFTER RECONSTITUTION: It is common practice to utilize the reconstituted solution within a few hours. If it is necessary to keep the reconstituted solution for more than a few hours, store the reconstituted solution under refrigeration (2° to 8°C). Under these conditions, the solution is stable for 60 days, and is suitable for use unless darkening or precipitation occurs.

HOW SUPPLIED
NDC 0046-0749-05–Each package provides: (1) One Secule® vial containing 25 mg of conjugated estrogens, USP, for injection (also lactose 200 mg, sodium citrate 12.2 mg, and simethicone 0.2 mg). The pH is adjusted with sodium hydroxide or hydrochloric acid. (2) One 5 mL ampul of sterile diluent with 2% benzyl alcohol in sterile water.

Premarin Intravenous (conjugated estrogens, USP) for injection is prepared by cryodesiccation.

SECULE®-Registered trademark to designate a vial containing an injectable preparation in dry form.

PATIENT INFORMATION
(Update Rev Date)

Premarin® Intravenous (conjugated estrogens, USP) for injection

Read this PATIENT INFORMATION which describes the benefit and major risks of your treatment, as well as how and when treatment should be used. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Premarin Intravenous (an estrogen mixture)?

- Estrogens increase the chances of getting cancer of the uterus.

  Report any unusual vaginal bleeding right away while you are taking Premarin. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, strokes, or dementia.

  Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens, with or without progestins, may increase your risk of dementia, based on a study of women age 65 years or older. You and your healthcare provider should talk regularly about whether you still need treatment with estrogens.

What is Premarin Intravenous?

Premarin Intravenous is a medicine that contains a mixture of estrogen hormones.

Premarin Intravenous is used to:

- treat certain types of abnormal uterine bleeding due to hormonal imbalance when your doctor has found no other cause of bleeding.

Who should not use Premarin Intravenous?

Premarin Intravenous should not be used if you:

- **have unusual vaginal bleeding that has not been evaluated by your healthcare provider.**

- **currently have or have had certain cancers.**
  Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use Premarin Intravenous.

- **had a stroke or heart attack in the past year.**

- **currently have or have had blood clots.**

- **currently have liver problems.**

- **are allergic to Premarin Intravenous or any of its ingredients.**
  See the end of this leaflet for a list of all the ingredients in Premarin Intravenous.

- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breast feeding**. The hormones in Premarin Intravenous can pass into your milk.

- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Premarin Intravenous works.

What are the possible side effects of Premarin Intravenous?

Premarin Intravenous is for short-term use only. However, the risks associated with Premarin tablets should be taken into account.

Less common but serious side effects include:
- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:
- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech

- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:
- Headache
- Breast tenderness
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:
- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus (“fibroids”)
- Vaginal yeast infections

These are not all the possible side effects of Premarin. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of getting a serious side effect with Premarin Intravenous?

- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about the safe and effective use of Premarin Intravenous

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Premarin Intravenous for conditions for which it was not prescribed. Do not give Premarin Intravenous to other people, even if they have the same symptoms you have. It may harm them. **Keep Premarin Intravenous out of the reach of children.**

This leaflet provides a summary of the most important information about Premarin Intravenous. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Premarin Intravenous that is written for health professionals. You can get more information by calling the toll free number 1-800-934-5556.

What are the ingredients in Premarin IV?

Premarin Intravenous for injection contains a mixture of conjugated estrogens, which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates: 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin. Premarin Intravenous for injection also contains lactose, sodium citrate, simethicone, and sodium hydroxide or hydrochloric acid in dry form. A sterile diluent containing benzyl alcohol in sterile water is provided for reconstitution. The reconstituted solution is suitable for intravenous or intramuscular injection.

Each Premarin Intravenous (conjugated estrogens, USP) for injection package provides 25 mg of conjugated estrogens, USP, in dry form and 5 mL of sterile diluent for intravenous or intramuscular use.

This product's label may have been revised after this insert was used in production. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

Wyeth®

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(Update W10411C006)
(Update ET01)
(Updated July 26, 2006)